HETEROATOM MEDIATED MODIFICATION OF REACTIVITY IN CARBON SKELETONS

BY

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To my Father

so close, yet so far

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DECEMBER, 1987

Chairman: Prof. Alan R. Katritzky
Major Department: Chemistry

The generation of α-aminocarbanions from secondary amines is a matter of long-standing interest. The usual way to generate such species involves a three-step sequence: protection of the amino proton, α-lithiation and electrophilic substitution followed by deprotection. As a superior alternative, carbon dioxide was investigated as a transient protecting group, which enabled electrophilic substitution at the α-position of tetrahydroquinoline and indoline in a one-pot sequence. However, the results show that the α-activating effect of lithium carbamates is small and requires strongly basic reagents for α-deprotonation.

Carbon dioxide has also been investigated as a protecting group for generating α-hydroxy carbanions. The α-activating power of lithium carbonates was found to be

indeed very small, even in cinnamyl system. In view of this, a trimethylsilyl group has been used as an easily removable α-activating auxilliary. Thus, 1-trimethylsilylmethanol *via* its lithium carbonate was successfully exploited to give a novel methanol dianion synthon in a one-pot sequence.

There are a few examples of thermal electrocyclic ring-opening of 1,2-dihydropyridines to the 1-azatrienes, a process considered uphill by thermodynamic considerations. It was of interest whether such ring-opening would be favored in N-vinyl-1,2-dihydropyridines. In the latter case, it was argued that the incipient 3-azatetraene may be induced into further non-degenarate reactions, thus driving the ring-opening equilibrium toward the right. Some novel N-cycloalkenyl-1,2-dihydropyridines were synthesized for this purpose and their thermal behavior studied. However, they preferably underwent oxidative fragmentation to the corresponding pyridine bases and no products arising out of their ring-opening was observed. Similar failures were also recorded for a 4-vinyl-1,2-dihydropyridine precursor.

CHAPTER I

GENERAL INTRODUCTION

1.1. Modification of Reactivity by Heteroatoms

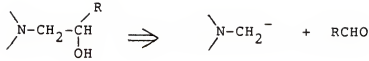
In general, saturated hydrocarbons are very inert molecules. They show little tendency to take part in most types of chemical reaction. Thus they do not behave as an electrophile nor can they be used as nucleophiles in a reaction. However, introduction of a heteroatom in an all-carbon framework dramatically alters the situation. By including a nitrogen atom (as in amines) or an oxygen atom (as in alcohols) many transformations can now be achieved at the carbon atoms as well as on the heteroatom. This is mainly due to the large electronegativity difference between carbon and the heteroatoms which induces considerable polarization in such carbon-heteroatom bonds.

Unsaturated carbon skeletons like alkenes and alkynes are more reactive than their saturated counterparts. By

virtue of their loosely bound π-electrons they undergo reactions with electrophiles and again, introduction of a heteroatom like nitrogen next to a π-bond greatly enhances their electrophilicity. The effect of the lone-pair on nitrogen is conjugatively transmitted to the π-electrons thus increasing their nucleophilic character which is well documented in enamine chemistry [82T1975, 82T3363].

1.2. Amines

The reactivity of the α-carbons in amines is dominated by nucleophilic attack at that center [68MI1] which shows that amines normally prefer a electropositive center next to the nitrogen. However, being more electronegative than carbon, the nitrogen atom in amines polarizes the C-N bonds to induce a partial positive character on the adjacent carbon, thus rendering the α-hydrogens somewhat acidic. This, in turn, opens up the possibility of generating a carbanionic center next to the nitrogen and hence to the prospect of electrophilic attack at that center. This type of reactivity umpolung at the α-carbon of amines was forseen by Seebach [79AG(E)239,77S357] and is most desirable since α-functionalization by nucleophilic attack has many limitations. For example, it would take a multistep sequence to construct a β-hydroxy amine skeleton which, instead, can be easily prepared in one step *via* the reaction of an α-amino carbanion with a suitable electrophile (Scheme 1.1).



Scheme 1.1

In practice, generation of α-amino carbanions proved to be a rather difficult task, especially for primary and secondary amines. In these cases the amino groups contain more acidic hydrogens and require protection during the α-deprotonation step. Here the principal problem lies in the choice of a suitable protecting group which should be easily introduced and subsequently removed as well as be inert to the deprotonating agent. However, with time, it became well recognized that the α-protons in amines are not acidic enough to be abstracted, even by strong bases and therefore needed additional activation, namely α-activation. This has been achieved in various ways, most commonly through the choice of an α-activating protecting group [84CRV471]. Yet another problem associated with α-amino carbanions is that, once generated, they face strong repulsion from the adjacent lone-pair on the nitrogen and their stability is greatly reduced. As a result, many α-amino carbanions show tendencies to undergo rearrangements whereby the negative charge is tranferrerd to the nitrogen atom, leading to a thermodynamically more stable situation.

Since α-functionalization in amines has been a matter of long-standing interest, research in the generation and utilization of α-amino carbanions continues. Now that generation of α-amino carbanions has been successfully demonstrated, greater stress has been applied to find novel yet simpler routes to these species.

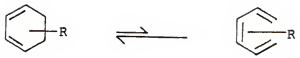
1.3. Alcohols

Since oxygen is more electronegative than carbon, the oxygen atom enjoys the greater share of the bonding electrons in a C-O bond. Hence the α-carbon atom in an alcohol attains some electropositive character. Being more electronegative than nitrogen, the degree of polarization in hydroxy derivatives is much more than in amines and nucleophilic attack on the α-carbon atom is much more facile in oxygenated compounds [71MI1]. On the other hand, inductive electron-withdrawal by oxygen makes the α-hydrogens acidic so that generation of an α-oxy carbanion is feasible. However, the generation of α-oxy carbanions faces similar problems as encountered with α-amino carbanions. Thus, the more acidic hydroxy proton needs prior protection and although the kinetic acidities of α-hydroxy protons are slightly higher than in amines, the process of α-activation is again necessary. The stability of α-oxy carbanions is even lower and they are very prone to 1,2-anionic migrations, most notably the Wittig rearrangement [70AG(E)763].

As a demonstration of reactivity umpolung at the α-carbon of alcohols, α-oxy carbanions has been successfully generated and utilized to construct key segments which otherwise require lengthy procedures. However, in contrast to the amines, reactivity umpolung at the α-carbon of hydroxy compounds has found less prominence since several other synthetic sequences are available which formally implement the concept. Nevertheless, α-oxy carbanions are synthetically important intermediates and are attractive targets for synthetic chemists.

1.4. Vinylic Amines

Pericyclic reactions are one of the most interesting classes of reactions associated with alkenes and dienes; of these, the thermal electrocyclic reactions of polyenes have created much interest [80MI1] both from the mechanistic and the synthetic viewpoints. Cyclic dienes have attracted considerable attention as substrates for thermal electrocyclic reactions. Suitable 1,3-cyclohexadiene moieties undergo 6π cycloreversion to the corresponding 1,3,5-hexatriene system (Scheme 1.2). Although this transformation is considered an equilibrium, the forward reaction can rarely be used preparatively due to unfavorable energetics [80MI2].

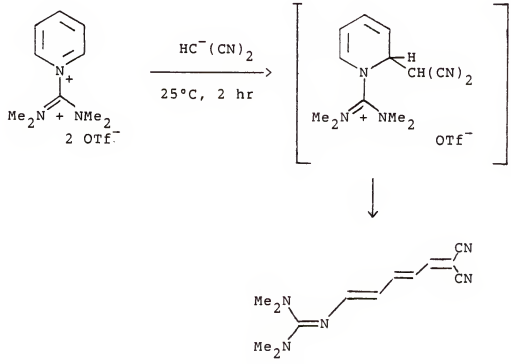


Scheme 1.2

The formation of 1,3-cyclohexadiene from cis-1,3,5-hexatriene has an activation enthalpy of 29.0 Kcal/mole [64JCS3080]. The heats of formation of 1,3-cyclohexadiene and cis-1,3,5-hexatriene are reported as 40.6 and 25.4 Kcal/mole, respectively [69CC833]. These figures establish the $\Delta H^{\neq}$ for the ring opening of cyclohexadiene at 44.2 Kcal/mole which means that very high temperatures would be necessary to achieve ring-opening of 1,3-cyclohexadiene type systems. Thus, in contrast to numerous instances of electrocyclizations of 1,3,5-hexatrienes, one finds only a few examples of cycloreversion in 1,3-cyclohexadiene systems.

In 1,3-cyclohexadiene, substitution of a methylene group by a heteroatom such as nitrogen transforms it to a 1,2-dihydropyridine which can be looked upon as a dienamine. Both enamines and dienamines are more polarized than their parent alkenes. Although they participate in pericyclic reactions, the reactions are mostly polar in nature and quite often occur in stepwise fashion. Thus it can be

expected that the diene moiety in 1,2-dihydropyridinies would be perturbed by the nitrogen so as to aid in its cycloreversion. Experimental evidence shows this not to be of considerable extent and 1,2-dihydropyridines are much more stable than the 1-azatrienes [80MI3]. However, in contrast to 1,3-cyclohexadienes, examples of ring-opening of 1,2-dihydropyridines are more numerous and the process is indeed facile in those cases where the resulting azatrienes enjoy extensive charge delocalization. This has been elegantly shown by Maas [85AG(E)511] (Scheme 1.3).



Scheme 1.3

The above reaction, together with several examples of the ANRORC (Addition of Nucleophile--Ring Opening--Ring Closure) type reactions of pyridinium salts [80S589] show that, given the proper scenerio, 1,2-dihydropyridines are much easier to ring-open than 1,3-cyclohexadienes.

1.5. Preview of the Work

In Chapter II of this dissertation, a novel methodology for the generation of α-carbanions from secondary amines is described. In that section, stress has been given to the role of the protecting group; also, the concept of transient α-activation *via* anionic protection has been introduced. The same concept was next applied to the generation of α-hydroxy carbanions (Chapter III) which in the process also saw the utilization of the trimethylsilyl group as an easily removable α-activating auxilliary.

In Chapter IV, thermal electrocyclic reactions of a cyclic dienamine, a 1,2-dihydropyridine were evaluated. The synthesis and thermal behavior of some novel N-cycloalkenyl-1,2-dihydropyridines have been investigated and their results are presented.

CHAPTER II

α-AMINOCARBANIONS

2.1. Introduction

In amines, the inductive electron withdrawal by nitrogen generates a small positive charge on the α-carbon, rendering the α-hydrogen(s) acidic. As a result, the generation of α-aminocarbanions becomes feasible and leads to the prospect of electrophilic substitution at the α-carbon of amines. However, the generation of α-aminocarbanions has several associated problems. Primary and secondary amines possess more acidic hydrogen(s) on the heteroatom and, in these cases, generation of α-aminocarbanions would require prior protection of the amino group. Furthermore, the α-aminocarbanions, once generated, experience strong repulsion from the adjacent lone-pairs on nitrogen, thus destabilizing them.

Chemical transformations at the α-carbon of an amine is a matter of long-standing interest and in this regard, α-aminocarbanions were expected to play a powerful role. Thus in the last decade much research has been devoted to the generation of α-aminocarbanions, as a result of which several α-aminocarbanion synthons are now available. These synthons have been critically assesed and several reviews have appeared on these and related topics [75AG(E)15,77S357, 78CRV275,79AG(E)239,80T2531,84CRV471,85MI1].

2.1.1. Indirect Routes to α-Aminocarbanions

Some α-aminocarbanions can be generated as their lithio salts without using an α-deprotonation step in the sequence. These methods are termed here as "indirect methods," which utilize either trans-metallation (usually tin-lithium exchange) or lithium-metalloid exchanges [80T2531]. In the latter class, the name "metalloid" implies elements such as S, Se, and the heavier members of the halogen family.

Tin-lithium exchange has been successfully utilized to generate α-lithio-tertiary amines. Thus the readily-available dialkylaminomethylstannanes **(2.1)**, on treatment with n-butyllithium, gave rise to the dialkylaminomethyllithium reagents **(2.2)**. The latter upon reaction with different electrophiles produced the expected

α-alkylated amines (2.3) (Scheme 2.1) [86TL2361, 84MI1, 71JA4027]. That this type of transmetallation produces a free organolithium (e.g. 2.2), and not any pentavalent "tin-ate" complex, can be nicely shown by ^{119}Sn-NMR studies [85TL1141,86JA2102].

$$R_2N\text{-}CH_2\text{-}SnBu_3 \xrightarrow{BuLi} R_2N\text{-}CH_2\text{-}Li \xrightarrow{E^+} R_2N\text{-}CH_2\text{-}E$$

(2.1) (2.2) (2.3)

Scheme 2.1

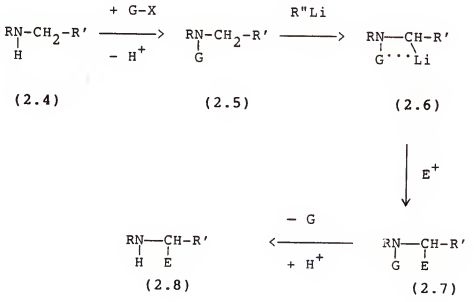
Although quite rewarding in its own merit, this transmetallation route suffers from a few drawbacks. The process fails completely when the α-carbon is either secondary or tertiary in nature [84MI1]. Similar transmetallations for α-stannyl-primary and -secondary amines are yet to be reported [85TL1141].

Lithium-metalloid exchange may not be a wise choice for generating α-lithioamines. The starting materials (e.g. α-haloamines) needed for this purpose are rather unstable and are often difficult to prepare.

2.1.2. Protection-Activation Route to α-Aminocarbanions

This section deals with the more direct approach toward α-aminocarbanions, formed as their lithio salts. We would focus our attention on the α-lithio secondary amines where this methodology has found considerable success. In the

"protection-activation" route, the α-lithioamines are generated by direct abstraction of an α-hydrogen using a strong lithiating base. In order to do so, the more acidic amino hydrogen needs protection. The protecting groups are so chosen that they are capable of performing two functions simultaneously. Firstly, the more acidic amino proton is protected from reacting with the lithiating base. Secondly, they play a major role in activating the α-position toward hydrogen abstraction. This process of α-activation is necessary since the α-hydrogens of amines are not acidic enough to be abstracted by strong bases. If "G" be such a hypothetical protecting-activating group, α-alkylation of a secondary amine can be visualized to occur as depicted in Scheme 2.2.



(2.4) (2.5) (2.6) (2.8) (2.7)

Scheme 2.2

The key step in the sequence in Scheme 2.2 is the formation of the α-lithio species (**2.6**) from **2.5**, since it involves the process of α-activation. There are several possibilities by which the protecting group (in **2.5**) could activate the α-position. According to Beak and Meyers [86ACR356], prior complexation of lithium (from the lithiating base) with "G" would activate the lithiating agent as well as direct the latter on to the α-carbon via a rigid chelate. In doing so, a partial dipole might also be created resulting in increased kinetic acidities of the α-protons (Figure 2.1).

Figure 2.1. α-Activation of Secondary Amines

In all probability the processes of prior complexation and dipolar activation would work in unison and complement each other. The α-lithio species once formed owes its stability to a great extent on the co-ordinating power of the protecting group so as to (partly) satisfy the co-ordination sites for lithium. For an all round success,

the protecting group itself should not contain any acidic hydrogen, should be inert to the metallating agent and, of course, be easily introduced and removed.

Based on these concepts several protecting-activating groups have been successfully employed in generating α-lithio secondary amines. Some of the versatile α-lithio secondary amine precursors are shown in Figure 2.2. A comprehensive picture can be obtained from Beak's recent review on this subject [84CRV471].

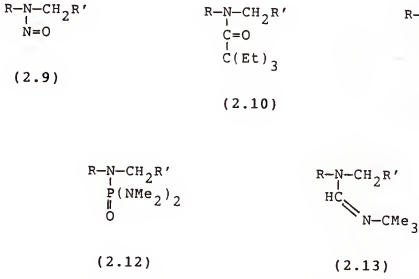


Figure 2.2. α-Lithio Secondary Amine Precursors

For the N-nitrosoamines (2.9) [75AG(E)15], resonance stabilization of the α-carbanion is thought to be the chief source of α-activation [78CRV275]. Lithium diisopropylamide (LDA) has been used as the lithiating agent. The remaining examples in Figure 2.2 operate on the "prior complexation-

activation" concept [86ACR356] and stronger metallating agents like alkyllithiums were necessary for their success. However, alkyllithiums are strong nucleophiles as well and the use of such strongly nucleophilic agents warrants that the protected center be sufficiently hindered so as to prevent attack at that position. Thus the sterically crowded triethylacetamides **(2.10)** [84JA1010], and triphenylacetamides **(2.11)** [83T1963] have been chosen to protect their carbonyl centers from any nucleophilic attack. By comparison, phosphonamides **(2.12)** [83T1963] and formamidines **(2.13)** [85MI1] are relatively inert to attacks by organolithiums.

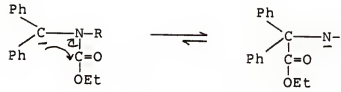
At present, the N-nitrosoamines **(2.9)** and the formamidines (2.13) stand out as the most useful precurssors to α-lithio secondary amines. Both such systems encourage α-lithiation on 1°, 2° and 3° carbons and alkylation has been achieved with a wide variety of electrophiles. However, the N-nitrosoamines are notoriously toxic and hazardous. The formamidines, on the other hand, are easy to prepare, non-toxic and can be deprotected (by hydrazinolysis or $LiAlH_4$ reduction) to liberate the α-alkylated secondary amines. In addition, chiral formamidines derived from secondary amines served as substrates for asymmetric α-alkylation and have

been utilized for the synthesis of various alkaloids in high (90-98%) enantiomeric excesses [87JA1263, 87JA1265, 86JOC3108, 86JOC3076]. The α-aminocarbanion precursors **2.10**-**2.12** require very harsh deprotection steps and are thus not of much practical use.

2.1.3. Carbon Dioxide as a Protecting-Activating Group

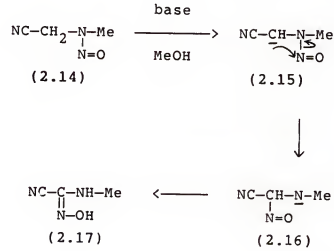
As just described, α-alkylation of secondary amines can be achieved in a three-step sequence: protection, α-lithiation and electrophile addition followed by deprotection (Scheme 2.2); the principal focus being in the α-lithiation step. In order to accomplish this, special protecting groups have been employed. In some cases (e.g. **2.10** and **2.11**), preparation of the protecting group itself involved multistep synthesis while in others, deprotection needed extreme conditions (e.g. **2.11** requires dissolving metal reduction) thereby limiting their synthetic utility.

An additional problem encountered in the generation of α-aminocarbanions is the 1,2-migration of the N-protecting group. This type of anionic migration is extremely facile since it involves an entropically favored three-membered transition state. The equilibrium in Scheme 2.3 demonstrates such a rearrangement [76CC339].



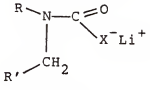
Scheme 2.3

Another example of such 1,2-anionic migration is found in the case of N-nitroso(2-methylamino)acetonitrile (2.14) (Scheme 2.4). In basic methanol, 2.14 gives rise to the α-carbanion (2.15) which triggers off a facile nitroso-transfer, ultimately leading to the amidoxime (2.17) [62HCA2426, 64HCA33, 78JOC3617]. Similar nitroso-transfer has also been observed during the α-lithiation of N-(t-butyl)-N-(nitroso)trimethylsilylmethylamine [77CB1852].



Scheme 2.4

This type of migration of the N-protecting group is aided by the fact that the nitrogen, in most cases, is attached to an electrophilic center (either a carbonyl for the amides or a nitroso for the N-nitrosoamines). On the other hand, such electrophilic centers on nitrogen is essential both for α-activation and easy deprotection. This requirement withholding, a decrease in the electrophilicity of the N-bound center appeared to be a viable solution to the 1,2-migration problem. An anionically protected amine, e.g. **(2.18)** was thus considered as the remedy (Figure 2.3).



(2.18)

Figure 2.3. Anionically Protected Secondary Amine

It was envisaged that the negative charge at the protected end of **2.18** would decrease the electrophilicity of the carbonyl group and hence, the N ⟶ C migration could be minimized. Furthermore, the N-bound center in **2.18** remains electronically protected from nucleophilic attack by the lithiating agent. The process of α-activation could still be operative through prior complexation of the lithiating agent

either to "X" or to the carbonyl oxygen. The biggest advantage of using **2.18** lies in the prospect of its facile deprotection. This should occur readily since the protecting group would be lost as a neutral molecule (O=C=X).

The proposed synthon **(2.18)** could possibly be made via the reaction of an N-lithio amine with a suitable cumulene of general stucture O=C=X (Scheme 2.5). In choosing the appropriate cumulene, preference should be given to those in which X is a heteroatom so that the negative charge in **2.18** is better accomodated. Also, a heteroatom at that position may be neccessary for the process of α-activation through prior complexation with the lithiating agent.

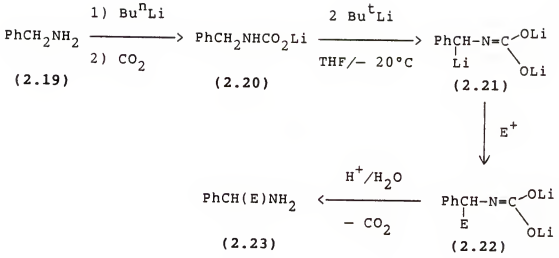
(2.18)

Scheme 2.5

One such cumulene which meets all these requirements is carbon dioxide. It is readily available, relatively non-toxic and has the proven ability as an electrophile. A thorough search of the literature revealed that various N-lithio derivatives of secondary amines react with CO_2 to

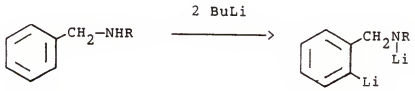
form the corresponding lithium carbamates [87H1333]. These salts, although stable in the absence of moisture, readily loose CO_2 on mild hydrolysis or simple heating [87H1333]. This latter property, we thought, could be efficiently exploited to achieve a very mild deprotection step. Given the hope that α-lithiation of lithium carbamates could be achieved, a novel synthon for α-aminocarbanions was in the offering.

In a preliminary study carried out by previous workers in this group, CO_2 has shown considerable promise as a protecting-activating group for α-lithiation of a primary amine. Benzylamine **(2.19)** was investigated as a model compound which formed its lithium carbamate **(2.20)** on being treated with n-butyllithium (1 equivalent) followed by CO_2. Treatment of **2.20** with two equivalents of t-butyllithium gave rise to the α-lithio species **(2.21)** which was subsequently trapped with various electrophiles (D_2O, CO_2, MeI, $PhCO_2Et$, Bu^tNCO, PhNCO) providing the α-substituted carbamates **(2.22)** (Scheme 2.6). The latter, without the need of isolation, was readily deprotected under acidic work-up to give the α-substituted benzylamines **(2.23)** in good yields [87S415]. As an added advantage, the whole set of operations can be executed in the same reaction vessel.



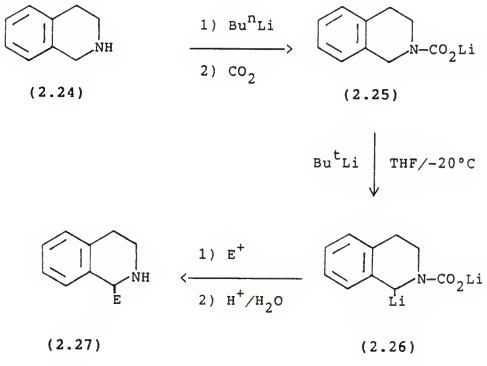
Scheme 2.6

The directing power of the lithium carbamate (**2.20**) can be well appreciated if one considers that mono- and disubstituted benzylamines undergo exclusive ortho-lithiation in the phenyl ring [71JOC1607,63JOC663, 63JOC3461,67JOC1479] (Scheme 2.7). For ortho-lithiation to occur in **2.20**, a seven-membered chelate would be neccesary; instead a more rigid five-membered chelate in **2.21** directs the lithiation at the benzylic carbon.



Scheme 2.7

Previous workers have also studied the lithium carbamate route for α-lithiation of a secondary amine, namely tetrahydroisoquinoline (**2.24**). Most gratifyingly, the derived lithium carbamate (**2.25**) underwent facile lithiation at the 1-position to produce the α-lithio species (**2.26**). The latter upon reaction with different electrophiles followed by acidic work-up directly afforded the 1-substituted tetrahydroisoquinolines (**2.27**) (Scheme 2.8) [86T2571]. Again, the whole sequence can easily be carried out in the same reaction vessel.



Scheme 2.8

With these preliminary results in hand, a detailed study of this novel α-lithiation process was most desirable.

2.1.4. Aims of the Work

The aim of the present investigation was to explore various other lithium carbamates as α-aminocarbanion synthons, in particular, those derived from unactivated secondary amines. α-Lithiation of benzylamine and tetrahydroisoquinoline via their lithium carbamates can be considered as examples where the respective α-hydrogens are fairly activated, being benzylic in nature. Therefore, the role of CO_2 in the α-activation step could not be critically assessed. Hence it was of interest to study the α-lithiation of those lithium carbamates where any kind of inductive activation of the α-hydrogens is absent. The secondary amines chosen for the study were 1,2,3,4-tetrahydroquinoline and indoline.

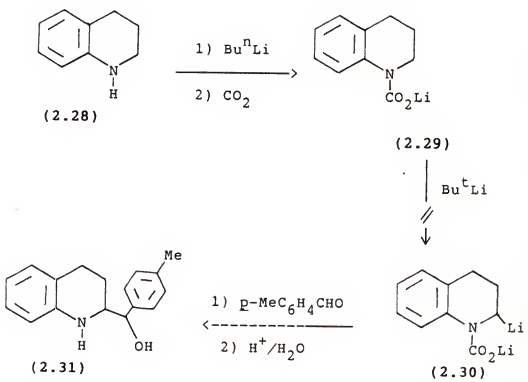
α-Lithiation of tetrahydroquinoline and indoline has previously been achieved only via their formamidines [81TL5119]. In that study, the respective α-lithio species were trapped with alkyl halides (MeI, BuI) and benzaldehyde to give the α-alkylated formamidines in good yields. However, deprotection of the latter required rather harsh

conditions such as refluxing with aqueous KOH or hydrazine, especially for the benzaldehyde adducts which could only be deprotected by $LiAlH_4$ in refluxing THF. In view of the mild deprotection procedure for the lithium carbamates, succesful α-lithiation of the tetrahydroquinoline and indoline via their lithium carbamates appeared as a potentially superior method for the α-functionalization of these amines.

2.2. Results and Discussion

2.2.1. α-Metallation Studies on Lithium 1,2,3,4-Tetrahydroquinolinyl Carbamate

1,2,3,4-Tetrahydroquinoline (**2.28**) was easily converted to its lithium carbamate (**2.29**) by sequential addition of n-butyllithium followed by CO_2 gas (Scheme 2.9). In order to achieve the desired α-lithiation, **2.29** was exposed to t-butyllithium in tetrahydrofuran. After 2 hrs at -20°C, p-tolualdehyde was added as the electrophile. However, after acidic work-up with 2N HCl, formation of the desired α-adduct **2.31** was not observed; the starting materials were recovered unchanged. Thus it was evident that the α-lithio species **2.30** was not generated under these conditions.

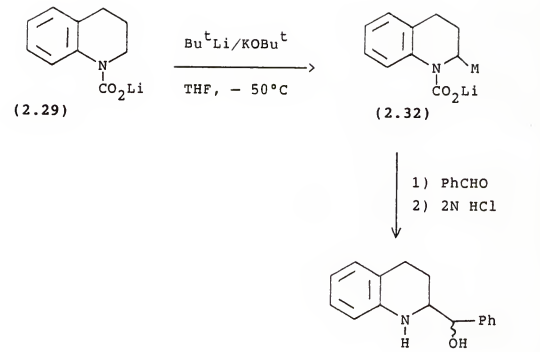


Scheme 2.9

In order to achieve the desired α-lithiation, **2.29** was subjected to various other reaction conditions. It was found that solvent had no effect on the lithiation process. Thus the reaction failed when carried out in ether as well as in hexane (heterogeneous system). Complexing agents [86TL331] like hexamethylphosphoramide (HMPA) or tetramethylethylenediamine (TMEDA) also had no effect on the reaction and in each case, the starting materials were recovered unchanged. These failures, however, shed some light on the role of CO_2 in the α-lithiation step: the lithium carbamate **2.29** had no perceptible activation toward

α-lithiation. At this stage it was felt that the source of α-activation for lithium carbamates lies somewhere else, probably in the use of a stronger metallating agent. This received some support from the recent studies by Schlosser [84TL741] on the superior metallating power of alkyllithiums in an admix with potassium alkoxides. More pertinent to the present study was the report by Ahlbrecht [84TL1353] who described the successful α-metallation of N-methyl tertiary amines using a mixture of potassium t-butoxide and s-butyllithium, otherwise a poor yielding process with alkyllithiums alone. On the basis of these reports, we proceeded to reinvestigate the α-metallation of the lithium carbamate **2.29** using Schlosser's mixed base system.

The lithium carbamate **2.29** was generated as described before in Scheme 2.9. When **2.29** was treated at −78°C with an equimolar mixture of t-butyllithium and potassium t-butoxide in tetrahydrofuran, a wine-red solution was immediately formed. Addition of benzaldehyde discharged this color and after stirring overnight at room temperature, the reaction was worked-up with 2N HCl. This time the crude product mixture afforded the desired α-adduct **2.33** in 55% yield as a mixture of diastereomers (Scheme 2.10).



(2.29) **(2.32)**

(2.33) (55%)
(erythro:threo = 40:60)

Scheme 2.10

Optimization of the reaction conditions gave the best results when t-butyllithium was used as the alkyllithium component and the metallation being carried out at -50°C for 2 hrs. The reaction worked best in tetrahydrofuran since the lithium carbamate **2.29** was found to be insoluble in other solvents such as hexane or ether.

The diastereomers of **2.33** were separated by careful column chromatography (silica gel) to give a 40:60 ratio of

erythro:threo isomers and were characterized individually by their ^{1}H and ^{13}C-NMR spectra. Their stereochemical assignments were based, tentatively, on the nature of the α-hydroxy proton in the ^{1}H-NMR spectra (200 MHz) (Fig. 2.4) and were in agreement with the trend which is observed for similar α-adducts of tetrahydroquinoline [81TL5119] and piperidine [79TL771, 85JOC1019]. According to these reports the α-hydroxy proton of the erythro-adducts usually appears at a more downfield region and with a lower coupling constant than that of the threo-isomers. Thus, in our hands, the product-isomer whose α-hydroxy proton appeared at δ 4.97 (d, J 6 Hz) was assigned to erythro-2.33; the corresponding proton for the other isomer was found at δ 4.97 (d, J 10 Hz) and was assigned to threo-2.33. In their ^{13}C-NMR spectra the α-hydroxy carbons were found at δ 75.1 and 76.0 wheras the α-amino carbons appeared at δ 41.6 and 43.0, respectively, for threo- and erythro-2.33. It should, however, be noted that both threo-2.33 (m.pt. 147°-149°C, from benzene - pet.ether) and erythro-2.33 (m.pt. 105°-107°C, from ether - pet.ether) were isolated as crystalline solids. This is in contrast to the only previous report [81TL5119] of their preparation where they were described as the hydrochloride salt (m.pt. 138°-141°C, from ether - ethanol) of the diastereomeric mixture.

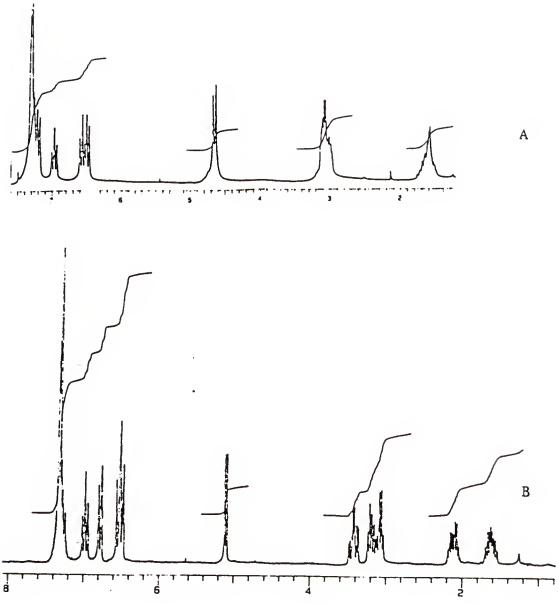
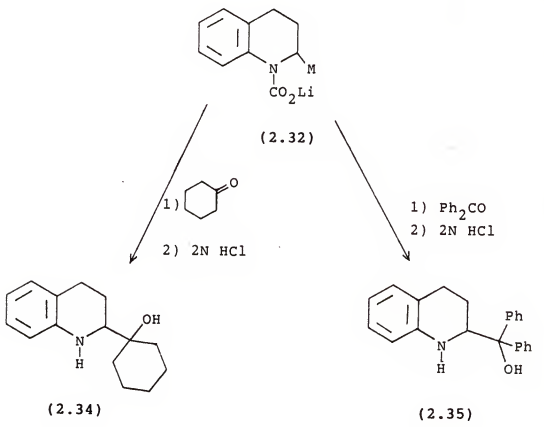


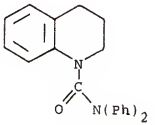
Figure 2.4. ^{1}H-NMR Spectra of the threo- and erythro-2.33
A = threo; B = erythro

The α-metallo species **2.32**, generated as in Scheme 2.10, reacted with other carbonyl electrophiles such as cyclohexanone and benzophenone to give the corresponding adducts **2.34** and **2.35** in 52 and 55% yield, respectively (Scheme 2.11). These novel adducts were each characterized by their ^{1}H and ^{13}C-NMR spectra as well as elemental (C,H,N) analyses.



Scheme 2.11

Our attempts at the α-functionalization of tetrahydroquinoline via **2.32** had its share of failures also. Of particular significance are the failures when diphenyl diselenide or dimethylformamide were used as electrophiles. These electrophiles are known to be highly lithiophilic and the failure in their reaction with **2.32** speaks in favor of formation of an α-potassio species, rather than an α-lithio species. Reaction of **2.32** with benzoyl chloride, methyl chloroformate or ethyl p-toluate produced complex product mixtures from which only a small amount of the desired products could be detected in their ^{1}H-NMR spectra. Interestingly, when diphenylcarbamoyl chloride was used as the electrophile, it produced **2.36** (35%), the product of N-carbamoylation. This latter result indicates partial cleavage of the N-protecting group in **2.29** during the α-metallation step which might account for the above failures as well as for the modest yields of the products **2.33-2.35** obtained so far.

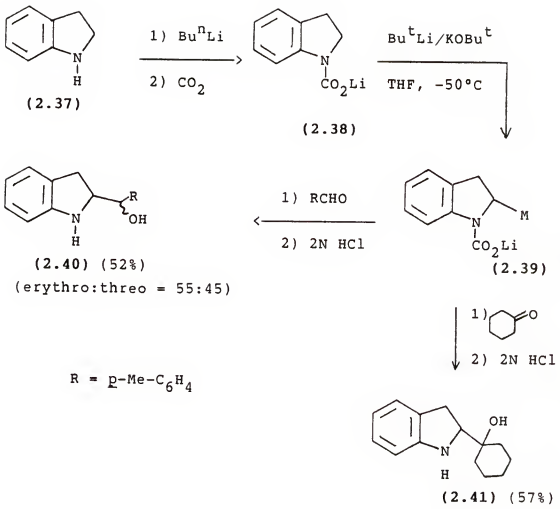


2.36

Similar results were obtained when methyl iodide was used as the electrophile. Although in the ^{1}H-NMR spectrum of the crude product the desired 2-methyltetrahydroquinoline could be observed, it was inseparable from the starting material due to very close R_f values. What could be separated by chromatography was shown to be N-methyltetrahydroquinoline (22%), the N-alkylation product.

2.2.2. α-Metallation Studies on Lithium Indolinyl Carbamate

Similar to the case of tetrahydroquinoline, the lithium carbamate (**2.38**) of indoline was prepared by sequential addition of n-butyllithium to the amine followed by CO_2 gas. As was expected, **2.38** did not undergo α-lithiation with t-butyllithium alone under a variety of reaction conditions. However, when **2.38** was treated at -78°C with an equimolar mixture of t-butyllithium and potassium t-butoxide in tetrahydrofuran, formation of the characteristic wine-red solution of the α-metallo species **2.39** was observed. The color was discharged upon addition of p-tolualdehyde and acidic work-up (with 2N HCl) after 12 hrs gave the α-adduct **2.40** in 52% yield (Scheme 2.12). The incipient α-metallo species **2.39** could also be trapped with cyclohexanone to give the adduct **2.41** in 57% yield (Scheme 2.12).



Scheme 2.12

The α-adduct **2.40** was obtained as a mixture of diastereomers. They were separated by careful column chromatography over silica-gel to give a 55:45 ratio of erythro:threo isomers. The stereochemical assignments were again based on the chemical shift and coupling constant of

their α-hydroxy proton in the ^{1}H-NMR spectra. In accordance to the literature data [81TL5119], the isomer whose α-hydroxy proton appeared at δ 4.85 (d, J 6 Hz) was assigned to erythro-**2.40**. Accordingly, the α-hydroxy proton for threo-**2.40** appeared at a relatively upfield position, δ 4.6 and with a slightly larger coupling constant (J 8 Hz). In their ^{13}C-NMR spectra, both the isomers showed the requisite number of carbons, the α-hydroxy carbons being found at δ 75.2 and 75.6, whereas the α-amino carbons appeared at δ 48.6 and 49.3, respectively, for threo- and erythro-**2.40**. Again it should be mentioned that the benzaldehyde α-adduct of indoline was previously reported [81TL5119] only as the hydrochloride salt of the diastereomeric mixture.

The novel cyclohexanone α-adduct **2.41** (m.pt. 108°-110°C, from ether - hexane) was obtained in 57% yield after column chromatography of the crude product mixture. It was characterized by its ^{1}H and ^{13}C-NMR spectra as well as by elemental (C,H,N) analysis.

Just like its tetrahydroquinoline counterpart, the α-metallo species **2.39** was also found to be inert to diphenyl diselenide and dimethylformamide, whereas reactions with ethyl p-toluate and methyl chloroformate gave complex product mixtures.

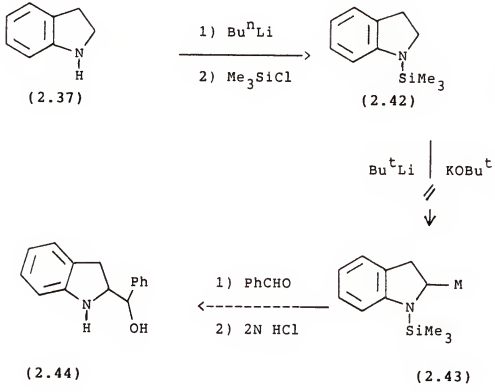
2.2.3. Role of Carbon Dioxide in the α-Metallation of Lithium Carbamates

In the previous two sections, a novel one-pot sequence for α-metallation of tetrahydroquinoline and indoline *via* their lithium carbamates was described. However, the principal question which remains unanswered is that concerning the role of lithium carbamates toward α-activation. In this section, we attempt to clarify this through some experimental observations.

We begin with Ahlbrecht's results [84TL1353] where the N-methyl groups of some tertiary amines were successfully metallated with Schlosser's mixed base system. In these cases, the substrate did not posses any α-activating group on the nitrogen. However, it should be noted that the proton in question was a primary hydrogen which would be expected to be more acidic than those encountered in our study, i.e. secondary hydrogens. Unfortunately, Ahlbrecht's report [84TL1353] provides no information on attempted α-metallation of secondary carbons in tertiary amines.

Unable to find a direct comparison, we set out to study the α-metallation of protected secondary amines where the protecting groups do not provide any kind of α-activation whatsoever. The substrate chosen for this purpose was the N-trimethylsilylindoline (**2.42**). The latter was prepared *in situ* from indoline (*n*-butyllithium - chlorotrimethylsilane)

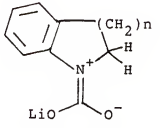
and treated first with a mixture of t-butyllithium and potassium t-butoxide followed by benzaldehyde as the electrophile (Scheme 2.13). However, after acidic work-up (with 2N HCl), none of the desired α-adduct (2.44) could be detected. Indoline and benzaldehyde were recovered unchanged.



Scheme 2.13

The above result, indirectly shows that lithium carbamates indeed have an α-activating effect. We believe that dipole creation (as in 2.45) is the major factor behind

such α-activation resulting in increased acidity of the α-protons. However, the extent to which this happens must be small since it required a very strong base like Schlosser's mixed base system for proton abstraction.



n = 1,2

2.45

2.3. Conclusions

Tetrahydroquinoline and indoline, via their lithium carbamates underwent successful α-metallation when treated with a mixture of t-butyllithium and potassium t-butoxide. The resulting α-metallo species were trapped with aldehydes and ketones to give the respective α-alkylated products in good yields, although alkyl halides and acyl chlorides failed in this respect. The nature of "M" in the α-metallo species 2.32 and 2.39 could not be ascertained at this stage. However, on the basis of Schlosser's [84TL741] and Ahlbrecht's [84TL1353] accounts, it was tentatively assigned

as potassium, although the results of attempted transmetallation to the α-lithio species remain inconclusive; thus treatment of 2.32 with lithium bromide, prior to the addition of benzaldehyde, led to much poorer yields of α-alkylation.

The advantages of the present methodology include a very mild deprotection step and the convenience of a one-pot operation. These score over the only reported procedure [81TL5119] for α-alkylation of tetrahydroquinoline and indoline which involved a conventional three-step sequence as well as very harsh deprotection conditions.

2.4. Experimental

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded on a Varian XL200 spectrometer. Chemical shifts for the protons are reported in δ (ppm) downfield from Me_4Si whereas those for the carbons were determined with reference to the solvent peaks ($CDCl_3$, δ 77.0 or DMSO-d_6, δ 39.5). The nature of the carbon signals in the ^{13}C-NMR spectra were determined by the Attached Proton Test [81CC150, 82JMR535]. Mass spectra were recorded on a AEI MS instrument attached to a DS 55 database. Elemental analyses (C,H,N) were performed by Dr. Roy W. King of this department. All

manipulations involving organolithium compounds were carried out in oven-dried (120°C, overnight) apparatus under a slight positive pressure of dry argon. Transferrring operations were done either by syringe techniques or *via* canula. Tetrahydrofuran (THF) and ether were freshly distilled from sodium-benzophenone ketyl. Chlorotrimethylsilane, hexamethylphosphoramide (HMPA) and tetramethylethylenediamine (TMEDA) were distilled from calcium hydride under reduced pressure and stored over molecular sieves. Petroleum ether (36°-60°C), hexane and triethylamine were distilled from calcium hydride and stored over potassium hydroxide. Column chromatography was carried out on MCB silica gel (230-400 mesh) and the solvents used for chromatography were routinely distilled prior to use.

General Procedure for α-Alkylation of Indoline and Tetrahydroquinoline

n-Butyllithium (2.5 M in hexanes, 2 ml, 5 mmole) was added dropwise at -78°C, under argon, to a solution of the amine (5 mmole) in dry THF (35 ml) in a 250 ml Schlenk type reactor. It was then slowly warmed to room temperature and dry CO_2 gas rapidly bubbled through it. The solution turned colorless (a colorless solution at this stage is vital for ultimate success; otherwise, poor yields were obtained). All volatile contents were then removed under 0.5 mm leaving a white powdery residue of the lithium carbamates. A preheated

(140°C, 0.5 mm, 2 hrs) sample of potassium t-butoxide (0.57 g, 5 mmole) was then quickly added, under argon, to the reactor. After redissolving in dry THF (40 ml), t-butyllithium (1.7 M in pentane, 3 ml, 5 mmole) was slowly added at -78°C. The resulting wine-red solution was stirred for 2 hrs at -50°C and the appropriate electrophile was then added at -78°C. Stirring was continued at room temperature for 12 hrs; the solvent was then removed at 0.5 mm and the residue treated with hydrochloric acid (2N, 10 ml). After gas evolution ceased, it was basified with solid sodium carbonate and was extracted with ethyl acetate or methylene chloride (3 x 20 ml). The combined organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent followed by column chromatography (silica-gel, 2-15% gradient of ethyl acetate in hexane containing 10-15% triethylamine) gave the products which were characterized according to the individual cases described below:

1-Phenyl-1-(1,2,3,4-tetrahydroquinolin-2-yl)carbinol **(2.33)**.

Yield 55%; erythro:threo = 40:60.

threo-**(2.33)**: R_f 0.5 (silica-gel, 10% ethyl acetate in hexane containing 10% triethylamine); m.p. 147-149°C (needles from benzene-pet.ether); Found: C, 80.52, H, 7.02, N, 5.80. $C_{16}H_{17}NO$ requires C, 80.30, H, 7.16, N, 5.85%. δ_H

($CDCl_3$/DMSO-d_6/D_2O) 1.6(2H, m), 3.1 (3H, m), 4.65 (1H, d, J 10 Hz), 6.4-6.6 (2H, m), 7.0 (1H, m) and 7.2-7.5 (6H, m). δ_C 22.0 ($\underline{C}H_2$), 36.6 ($\underline{C}H_2$), 41.6 ($\underline{C}H$-N), 75.1 ($\underline{C}H$-OH), 112.4 (aryl $\underline{C}H$), 113.7 (aryl $\underline{C}H$), 119.6 (aryl $\underline{C}$), 125.6 (aryl $\underline{C}H$), 125.7 (aryl $\underline{C}H$), 125.8 (aryl $\underline{C}H$), 126.7 (aryl $\underline{C}H$), 130.1 (aryl $\underline{C}H$), 142.8 (aryl $\underline{C}$) and 143.6 (aryl $\underline{C}$).

erythro-**(2.33)**: R_f 0.4 (silica-gel, 10% ethyl acetate in hexane containing 10% triethylamine); m.p. 105-107°C (needles from ether-pet.ether); Found: C, 80.30, H, 7.31, N, 5.55. $C_{16}H_{17}NO$ requires C, 80.30, H, 7.16, N, 5.85%. δ_H ($CDCl_3$/D_2O) 1.65 (1H, m), 2.2 (1H, m), 3.0 (1H, m), 3.2 (1H, m), 3.4 (1H, m), 4.97 (1H, d, J 6 Hz), 6.4-6.7 (3H, m), 6.9 (1H, m) and 7.2-7.3 (5H, m). δ_C 21.7 ($\underline{C}H_2$), 39.2 ($\underline{C}H_2$), 43.0 ($\underline{C}H$-N), 76.0 ($\underline{C}H$-OH), 114.3 (aryl $\underline{C}H$), 116.7 (aryl $\underline{C}H$), 120.4 (aryl $\underline{C}$), 126.3 (aryl $\underline{C}H$), 127.1 (aryl $\underline{C}H$), 127.4 (aryl $\underline{C}H$), 128.1 (aryl $\underline{C}H$), 129.2 (aryl $\underline{C}H$), 142.5 (aryl $\underline{C}$) and 145.6 (aryl $\underline{C}$).

1-(1,2,3,4-Tetrahydroquinolin-2-yl)cyclohexanol **(2.34)**.

R_f 0.5 (silica-gel, 12% ethyl acetate in hexane containing 10% triethylamine); yield 52%; viscous oil; M^+ (HRMS) found: 231.1632. $C_{15}H_{21}NO$ requires 231.1624. δ_H ($CDCl_3$/D_2O) 1.4-1.7 (11H, m), 2.2-2.3 (1H, m), 2.7 (1H, m), 3.3 (1H, m), 3.55 (1H, m), 6.4-6.6 (2H, m) and 6.9-7.0 (2H, m). δ_C 22.0 ($\underline{C}H_2$), 22.2 ($\underline{C}H_2$), 25.8 ($\underline{C}H_2$), 34.1 ($\underline{C}H_2$), 37.6

($\underline{C}H_2$), 39.2 ($\underline{C}H_2$), 44.5 ($\underline{C}H$-N), 73.8 ($\underline{C}$-OH), 113.9 (aryl $\underline{C}H$), 115.6 (aryl $\underline{C}H$), 119.8 (aryl $\underline{C}$), 127.6 (aryl $\underline{C}H$), 131.5 (aryl $\underline{C}H$) and 145.3 (aryl $\underline{C}$).

1,1-Diphenyl-(1,2,3,4-tetrahydroquinolin-2-yl)carbinol **(2.35).**

R_f 0.5 (silica-gel, 10% ethyl acetate in hexane containing 10% triethylamine); m.p. 128-129°C (plates from ether-hexane); Found: C, 83.81, H, 6.97, N, 4.09. $C_{22}H_{21}NO$ requires C, 83.78, H, 6.71, N, 4.44%. δ_H ($CDCl_3/D_2O$) 1.8 (1H, m), 2.1 (1H, m), 3.0 (1H, m), 3.4 (1H, m), 4.05 (1H, m), 6.2-6.55 (3H, m), 6.95 (1H, m) and 7.1-7.8 (10H, m). δ_C 24.1 ($\underline{C}H_2$), 39.6 ($\underline{C}H_2$), 43.9 ($\underline{C}H$-N), 81.5 ($\underline{C}$-OH), 114.4 (aryl $\underline{C}H$), 116.4 (aryl $\underline{C}H$), 118.9 (aryl $\underline{C}$), 125.8 (aryl $\underline{C}H$), 126.1 (aryl $\underline{C}H$), 126.2 (aryl $\underline{C}H$), 127.8 (aryl $\underline{C}H$), 128.0 (aryl $\underline{C}H$), 130.8 (aryl $\underline{C}H$), 145.3 (aryl $\underline{C}$), 146.3 (aryl $\underline{C}$) and 147.8 (aryl $\underline{C}$).

1-(Diphenylcarbamoyl)-1,2,3,4-tetrahydroquinoline **(2.36)**

R_f 0.6 (silica-gel, 10% ethyl acetate in hexane containing 10% triethylamine); yield 35%; m.p. 120-122°C (needles from ether-hexane); Found: C, 80.50, H, 6.23, N, 8.19. $C_{22}H_{20}N_2O$ requires C, 80.46, H, 6.14, N, 8.53%. δ_H ($CDCl_3$) 1.9 (2H, m), 2.5 (2H, m), 3.6 (2H, m), 6.8-7.3 (13H,

m) and 7.4 (1H, d, J 12 Hz). δ_C ($CDCl_3$) 23.4 ($\underline{C}H_2$), 26.5 ($\underline{C}H_2$), 45.4 ($\underline{C}H_2$), 122.5 (aryl $\underline{C}H$), 123.3 (aryl $\underline{C}H$), 124.8 (aryl $\underline{C}H$), 125.1 (aryl $\underline{C}H$), 126.0 (aryl $\underline{C}H$), 128.1 (aryl $\underline{C}H$), 128.7 (aryl $\underline{C}H$), 129.8 (aryl $\underline{C}$), 138.7 (aryl $\underline{C}$), 143.9 (aryl $\underline{C}$) and 159.3 ($\underline{C}$=O).

1-[(4'-methyl)phenyl]-1-(indolin-2-yl)carbinol **(2.40)**.

yield 52%; erythro:threo = 55:45.

threo-**(2.40)**: R_f 0.4 (silica-gel, 15% ethyl acetate in hexane containing 15% triethylamine); m.p. 130-133°C (reprecipitated from chloroform-hexane); M^+ (HRMS) found: 239.1331. $C_{16}H_{17}NO$ requires 239.1310. δ_H ($CDCl_3/D_2O$) 2.3 (3H, s), 3.0-3.3 (2H, m), 3.55 (1H, m), 4.6 (1H, d, J 8 Hz), 6.5-6.7 (2H, m) and 7.0-7.4 (6H, m). δ_C 20.4 ($\underline{C}H_3$), 48.6 ($\underline{C}H$-N), 49.1 ($\underline{C}H_2$), 75.2 ($\underline{C}H$-OH), 108.9 (aryl $\underline{C}H$), 117.6 (aryl $\underline{C}H$), 125.4 (aryl $\underline{C}H$), 126.0 (aryl $\underline{C}H$), 126.9 (aryl $\underline{C}H$), 128.0 (aryl $\underline{C}H$), 129.9 (aryl $\underline{C}$), 136.0 (aryl $\underline{C}$), 139.9 (aryl $\underline{C}$) and 151.3 (aryl $\underline{C}$).

erythro-**(2.40)**: R_f 0.3 (silica-gel, 15% ethyl acetate in hexane containing 15% triethylamine); m.p.123-125°C (reprecipitated from benzene-pet.ether); M^+ (HRMS) found: 239.1316. $C_{16}H_{17}NO$ requires 239.1310. δ_H ($CDCl_3/D_2O$) 2.35 (3H, m), 3.5-3.7 (3H, m), 4.85 (1H, d, J 6 Hz), 6.5-6.65 (2H, m) and 7.0-7.3 (6H, m). δ_C 21.1 ($\underline{C}H_3$), 49.3 ($\underline{C}H$-N),

49.7 ($\underline{C}H_2$), 75.6 ($\underline{C}H$-OH), 110.0 (aryl $\underline{C}H$), 118.5 (aryl $\underline{C}H$), 125.0 (aryl $\underline{C}H$), 126.5 (aryl $\underline{C}H$), 128.1 (aryl $\underline{C}H$), 128.6 (aryl $\underline{C}$), 129.0 (aryl $\underline{C}H$), 137.3 (aryl $\underline{C}$), 139.5 (aryl $\underline{C}$) and 152.2 (aryl $\underline{C}$).

1-(Indolin-2-yl)cyclohexanol (2.41).

R_f 0.5 (silica-gel, 15% ethyl acetate in hexane containing 15% triethylamine); yield 57%; m.p. 108-110°C (needles from ether-hexane); Found: C, 77.36, H, 9.03, N, 6.14. $C_{14}H_{19}NO$ requires C, 77.38, H, 8.81, N, 6.45%. δ_H ($CDCl_3/D_2O$) 1.3-1.8 (10H, m), 3.25 (1H, t, $\underline{J}$ 7 Hz), 3.6 (2H, d, $\underline{J}$ 7 Hz), 6.6-6.7 (2H, m) and 7.0-7.3 (2H, m). δ_C 21.6 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 33.8 ($\underline{C}H_2$), 34.4 ($\underline{C}H_2$), 48.8 ($\underline{C}H_2$), 52.9 ($\underline{C}H$-N), 73.6 ($\underline{C}$-OH), 109.6 (aryl $\underline{C}H$), 118.1 (aryl $\underline{C}H$), 126.3 (aryl $\underline{C}H$), 127.9 (aryl $\underline{C}H$), 128.5 (aryl $\underline{C}$) and 152.5 (aryl $\underline{C}$).

CHAPTER III

α-HYDROXYCARBANIONS

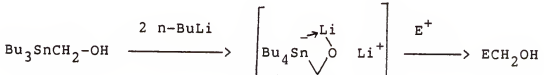
3.1. Introduction

In alcohols, the inductive electron withdrawal by oxygen induces a polarization of the carbon-oxygen bond. As a result, the α-carbon bears a small positive charge, rendering the attached hydrogens acidic. This could allow the generation of an α-hydroxycarbanion, leading to the possibility of electrophilic substitution at the α-carbon atom of the alcohol. In practice, however, α-hydroxy carbanions are very difficult to generate. First, the more acidic hydroxyl proton needs suitable protection. A more severe problem appears to be the instability of carbanions adjacent to oxygen. Such carbanions, once generated, experience strong repulsion from the oxygen lone pairs making them energetically unfavorable. Hence, α-hydroxycarbanions, or their synthons, remain as challenging targets to synthetic chemists.

α-Hydroxycarbanions (or their synthons) hold tremendous promise in their synthetic utility. Such synthons offer easy access to 1,3- and 1,4-dihydroxy carbon fragments which are key segments in numerous antibiotics and, until now, have only been made by lengthy synthetic operations.

3.1.1. Indirect Routes to α-Hydroxy Carbanions

The α-hydrogens of an alcohol are not acidic enough to be abstracted by a strong base. Therefore, indirect methods have been adopted to generate α-hydroxy carbanion synthons. The most notable approach is the transmetallation (tin-lithium) between tributylstannylmethanol **(3.1)** and n-butyllithium which was reported by Seebach [80CB1290]. This actually gives rise to a pentavalent "tin-ate" complex **(3.2)** (and not $LiCH_2OLi$) [80CB1290] which reacts with electrophiles to yield the α-substituted methanol derivatives (Scheme 3.1).



(3.1) **(3.2)**

Scheme 3.1

Lithium-metalloid exchange (e.g. reductive cleavage of monothioketals [84JA1130] or lithiodehalogenation of α-chloro ethers [64TL1503]) have also been used in generating α-lithio ethers but with limited success.

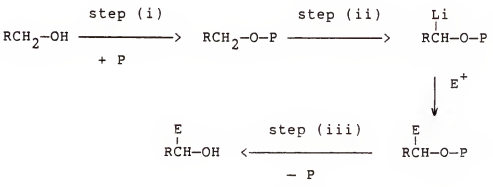
3.1.2. Protection-Activation Route to α-Hydroxycarbanions

The protection-activation route to α-hydroxycarbanions is a direct approach to α-hydroxycarbanion synthons. This involves three distinct steps (Scheme 3.2):

i) protection of the more acidic hydroxyl proton

ii) α-lithiation and subsequent alkylation with an electrophile, and finally

iii) deprotection of the hydroxy group.

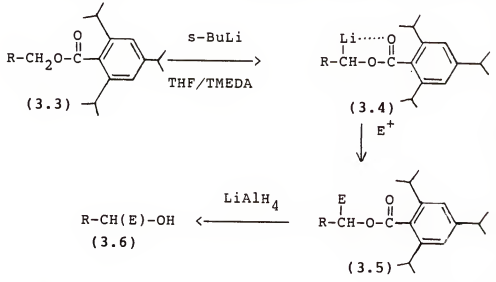


P = Protecting Group

Scheme 3.2

The crucial step in this sequence is the generation of the α-lithio species via lithium--α-hydrogen exchange. Since the α-hydrogen(s) of alcohols are not sufficiently acidic to be abstracted by strong base the process of α-lithiation requires additional activation. This can be achieved in various ways. The most common practice is to choose a

choose a suitable protecting group which simultaneously protects the hydroxy function and directs the lithiation on to the α-carbon atom. As would be expected, the choice of an appropriate protecting group is vital to the overall success of the process. This has been nicely demonstrated by Beak in his study on the α-lithiation of methanol and ethanol via their aryl esters (3.3) [77JA5213] (Scheme 3.3). In that report, the alcohol was first protected in the form of a highly hindered ester (3.3). α-Lithiation was achieved with s-butyllithium in presence of tetramethylethylenediamine to form the α-lithio species 3.4. Alkylation of the latter, followed by deprotection with lithium aluminum hydride, liberated the α-alkylated alcohols 3.6. Thus, the α-lithio species (3.4) behaved as an α-hydroxy carbanion equivalent.

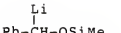


R = H, CH_3

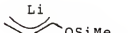
Scheme 3.3

Several features of this work are worthy of discussion. It should be noted that a highly hindered aryl group was used. This was necessary to prevent any nucleophilic attack on the carbonyl group of the aryl ester (3.3). Ironically, this became a serious problem in the latter stage when deprotection of 3.5 by conventional hydrolysis could not be achieved. A very harsh deprotection step involving $LiAlH_4$ had to be employed which is a serious drawback to this method. Nevertheless, the α-lithiation step (3.3 ——> 3.4) deserves special attention since it involves the process of α-activation. According to Beak, α-activation is derived through a "prior complexation" phenomenon where the carbonyl oxygen of (3.3) first coordinates with the lithiating base (s-butyllithium). This evidently directs the delivery of the s-butyl residue on to the α-hydrogens of 3.3. Similar arguments have been forwarded to explain the regio- and stereochemistry of various lithiation processes [86ACR356].

α-Lithiation of an alcohol is much easier when an activating (mesomeric) group is present in the α-position. Thus upon treatment with a strong base (t-butyllithium) benzyltrimethylsilyl ether gives rise to the α-lithio species (3.7) [74JA3214]. Allyl silyl ethers can also be metallated to generate the delocalized lithio species (3.8) [76JOC3620].

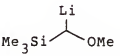


(3.7)

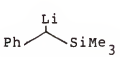


(3.8)

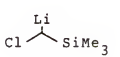
In recent years, great strides have been made in the utilization of silicon in organic synthesis [79MI1, 82MI1]. Organosilicon chemistry has shown two general trends. A silicon atom usually favors a positive charge "beta" to itself whereas it is capable of stabilizing an α-carbanion. Both these effects are due to the availability of d-orbitals on silicon. Thus the negative charge on an α-silyl carbanion can be effectively delocalized into the vacant d-orbitals of silicon. This has been amply demonstrated by Magnus who led the field in the application of α-silyl carbanions [80MI4]. A plethora of α-silyl carbanions are currently known, many of which also possess an α-heteroatom. Some of these, which have been useful to synthetic chemists, are shown below [80MI4].



(3.9)



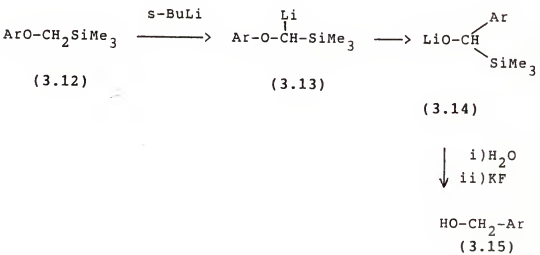
(3.10)



(3.11)

To us, the most encouraging example was that of α-lithio trimethylsilylmethyl methyl ether (**3.9**) [79CC822, 82OM553], since it shows that an α-trimethylsilyl group can also provide enough activation to generate α-oxy carbanions. The α-lithio species (**3.9**) was shown to react with carbonyl electrophiles (aldehydes and ketones) and the derived products were generally obtained in fair to good yields [82OM553].

Returning to the problems associated with α-oxycarbanions, one is faced with the facile 1,2-migration these species undergo via the Wittig rearrangement [70AG(E)763]. Thus, in sharp contrast to the α-lithio-methyl ether derivative (**3.9**), the corresponding α-lithio-aryl ether species (**3.13**) undergoes Wittig rearrangement when kept at room temperature [82JOC5051] (Scheme 3.4).



(**3.12**) (**3.13**) (**3.14**) (**3.15**)

Scheme 3.4

1,2-Anionic migrations in α-oxycarbanions are also common. Thus, both 1,2-acyl migration (e.g. **3.16** ⟶ **3.17**) [81JOC2363] and 1,2-phosphoryl migration (e.g. **3.18** ⟶ **3.19**) [80S289, 76TL47] have been reported for the respective α-oxycarbanions (Scheme 3.5). These rearrangements involve the transposition of the oxygen protecting group to the α-carbon. Therefore, the choice of an appropriate protecting group is of utmost importance for generating an α-oxy carbanion, especially <u>via</u> the protection-activation methodology.

(3.16) **(3.17)**

(3.18) **(3.19)**

Scheme 3.5

The current status of the synthetic art concerning α-hydroxycarbanions can be summarized as follows:

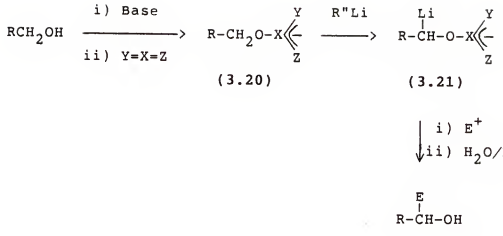
a) In the absence of a suitable activating group, α-hydroxycarbanions are very difficult to generate.

b) Once generated, α-oxycarbanions tend to undergo 1,2-migrations either via the Wittig rearrangement or by a 1,2-anionic shift.

These limitations are borne out by the experimental facts; until now only two α-hydroxy carbanion synthons, **(3.2)** and **(3.4)**, have been reported which are derived from unactivated alcohols.

3.1.3. Carbon Dioxide as a Protecting-Activating Group

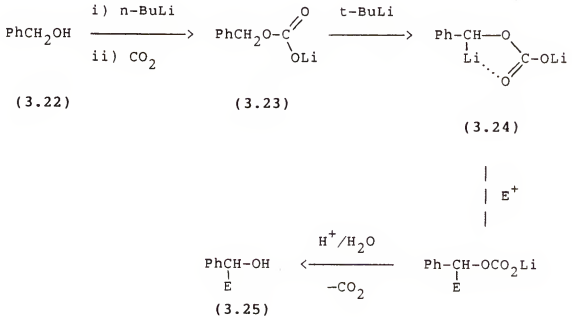
The 1,2-migrations, which are so problematic in the generation of α-oxy carbanions, could be minimized, in principle, if α-lithiation of anionically protected alcohols could be achieved. A proposed sequence is shown in Scheme 3.6. First the alcohol is protected by using a suitable protecting group (preferably a cumelene, Y=X=Z) so as to generate an anionically protected species like **3.20**. Successful α-deprotonation of **3.20** would give rise to the α-lithio species **3.21**, in which any 1,2-anionic migration would be electronically disfavored. Alkylation of **3.21** followed by simple hydrolysis would afford the desired α-alkylated alcohols.



Scheme 3.6

Earlier in section 2.2.3, carbon dioxide was introduced as a novel protecting group for amines. The resulting lithium carbamates proved to be useful substrates for α-lithiation of amines. Carbon dioxide appeared equally promising as a protecting group for alcohols. The derived hemicarbonate salts are very unstable in presence of moisture and rapidly lose carbon dioxide to return to the alcohol. In spite of their facile deprotection, the inherent instability of the hemicarbonates has restricted their synthetic utility as protected alcohols. To us, however, the hemicarbonate salts appeared ideally suited for α-lithiation studies: (a) carbon dioxide is a non-toxic, cheap commercial material, (b) the hemicarbonate salts aptly qualify as anionically protected alcohols and (c) their deprotection would be extremely rapid in the presence of aqueous acid.

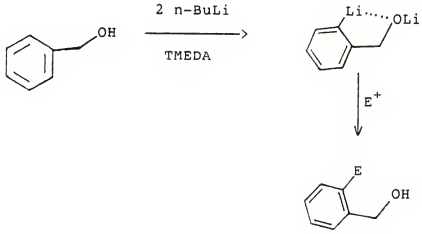
The above hypothesis has already been put to test by previous workers in this group. Benzyl alcohol (3.22) was chosen by those workers as the model hydroxy compound: treatment of this alcohol with n-butyllithium followed by CO_2 readily gave the corresponding lithium carbonate (3.23). When exposed to t-butyllithium, the latter underwent smooth metallation giving rise to the α-lithio species (3.24) which was trapped with different electrophiles (D_2O, CH_3I, CO_2, $PhCO_2Et$, Ph_2CO). Deprotection occurred spontaneously during acidic work-up and the α-alkylated benzyl alcohols (3.25) were isolated in fair to good yields [87S415] (Scheme 3.7). As an added advantage, the entire sequence was carried out in the same reaction vessel.



(3.22) (3.23) (3.24) (3.25)

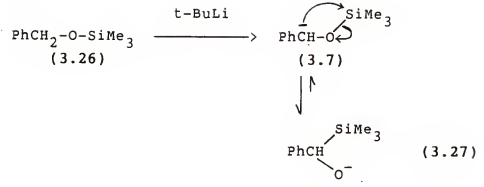
Scheme 3.7

Successful α-lithiation of lithium benzyl carbonate **(3.23)** is in sharp contrast to Seebach's study [80CB1304], the latter showing that benzyl alcohol on treatment with two equivalents of n-butyllithium afforded ortho-lithiation on the phenyl ring (Scheme 3.8).



Scheme 3.8

In this context, α-lithiation of benzyltrimethylsilyl ether **(3.26)** is also worthy of discussion. α-Lithiation of **3.26** can be achieved with t-butyllithium to produce the α-lithio species **(3.7)**, which however, undergoes a rapid 1,2-silyl migration as shown in Scheme 3.9 [74JA3214]. Such 1,2-migration was completely suppressed during the α-lithiation of lithium benzyl carbonate **(3.23)**.



Scheme 3.9

3.1.4. Aims of the Work

As discussed above, anionically protected alcohols have been introduced as superior substrates for α-lithiation and initial results with benzylalcohol via its lithium carbonate have shown considerable promise [87S415]. However, benzylalcohol is regarded as an activated system since the α-carbanion is stabilized by the adjacent phenyl group. Therefore, in the present work, it was our aim to probe into the limits of α-lithiation on lithium carbonates and for possible extension of this methodology to other alcohols.

The lithium carbonate of methanol was chosen as the primary target, for two main reasons. Firstly, α-lithiation would generate a primary carbanion in this case. Any other alcohol would give rise to either a secondary or a tertiary carbanion which are more difficult propositions, due to electronic as well as steric reasons. Secondly, α-lithiation studies on lithium methyl carbonate would provide a direct comparison with Beak's aryl ester methodology [77JA5213] depicted in Scheme 3.3. The role of the lithium carbonates,

if any, in the process of α-activation could thus be properly evaluated.

α-Lithiation of 1-trimethylsilylmethanol (via its lithium carbonate) appeared very promising for two main reasons. Firstly, the trimethylsilyl group has the proven ability to stabilize an α-carbanion. Secondly, a judicious choice of the electrophile would enable the trimethylsilyl auxilliary to be readily removed from the product. The latter prediction has strong literature precedents [74ACR77] in that a silicon atom is extremely labile when adjacent to carbonyl functions. Thus the successful α-lithiation of lithium 1-trimethylsilylmethyl carbonate would formally constitute the generation of a methanol dianion synthon.

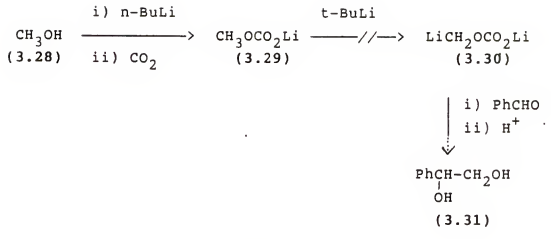
α-Lithiation of allylic alcohols has been the subject of numerous synthetic efforts in the past and present [84AG(E)932]. The generated α-carbanions can be effectively delocalized to the γ-carbon and, as such, varying degrees of selectivity (α vs. γ) are observed in the alkylation of these anions. Several oxygen protecting groups with varying co-ordinating powers have been investigated to control this selectivity [84AG(E)932]. In this perspective it was of considerable interest to investigate the directing power of

an allyl lithium carbonate. A strong chelating effect (five-membered chelate) from the carbonate function would be expected to increase the proportion of α-alkylation over the γ-attack. The extent to which this selectivity could be achieved was the principal objective in this case.

3.2. Results and Discussion

3.2.1. α-Lithiation Studies on Lithium Methyl Carbonate

Lithium methyl carbonate (**3.29**) was prepared in a manner similar to that of benzyl alcohol. Thus methanol (**3.28**) on treatment with n-butyllithium followed by carbon dioxide produced the lithium methyl carbonate (**3.29**) (Scheme 3.10). α-Lithiation of **3.29** was attempted with t-butyllithium in tetrahydrofuran at -20°C for 2 hrs. Subsequent addition of benzaldehyde followed by acidic work-up did not afford the desired 1,2-diol (**3.31**), benzaldehyde being recovered unchanged. A repeat reaction replacing benzaldehyde with ethyl benzoate failed, as well. Addition of HMPA or TMEDA to the reaction mixture also showed no promise; it was inferrred that the desired lithium lithiomethyl carbonate (**3.30**) was not formed under these conditions.



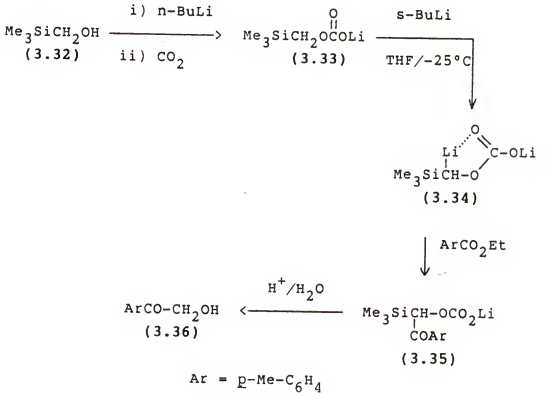
Scheme 3.10

A comparison of these results with Beak's aryl ester methodology (cf. Scheme 3.3) shows that the lithium carbonates have no perceptible α-activating effects. Thus it became evident that the hemicarbonate route to α-oxy carbanions can be applied only to activated systems. This led to the prospect of utilizing a trimethylsilyl group as an easily removable α-activating auxilliary.

3.2.2. α-Lithiation Studies on Lithium Trimethylsilylmethyl Carbonate

Commercially available 1-trimethylsilylmethanol (3.32) was easily converted to its lithium carbonate (3.33) following the standard procedure (n-butyllithium - CO_2). The latter was then treated with s-butyllithium in

tetrahydrofuran at -78°C. After stirring the virtually colorless solution for 2 h at -25°C, ethyl p-toluate was added as the electrophile and the resulting mixture stirred at room temperature for 8 hrs. Subsequent work-up with 10% aqueous hydrochloric acid afforded the α-hydroxyacetophenone derivative (3.36) in 68% yield (Scheme 3.11). The use of s-butyllithium in the metallation step was found to be essential as inferior yields were obtained when n-butyllithium or t-butyllithium were used.



Scheme 3.11

Formation of the α-hydroxyketone (3.36) can be rationalized via the intermediacy of the α-lithio species (3.34). Reaction of 3.34 with the ester electrophile presumably led to the α-silyl ketone derivative (3.35), which on hydrolysis lost CO_2 with concommitant protiodesilylation to give the hydroxymethylketone (3.36) (Scheme 3.11). The facile desilylation of 3.35 is to be expected since α-silyl carbonyl compounds are known to be readily desilylated upon hydrolysis [74ACR77].

Other carbonyl electrophiles reacted in the same way as ethyl p-toluate. The results are summarized in Table 3.1. Thus N,N-dimethylbenzamide and benzoyl chloride led to α-hydroxyacetophenone, as expected. The low yield obtained with benzoyl chloride was probably caused by undesired side reaction involving metal-halogen exchange. Benzonitrile was also successfully employed as the electrophile; the intermediate imine adduct hydrolyzed to the ketone on acidic work-up. Quite significant are the results when α,β-unsaturated esters were used as electrophiles (entries 5 and 6, Table 3.1). In both cases, carbonyl addition was the exclusive pathway giving rise to the hydroxymethyl vinyl ketones. The 1,4-addition mode was not observed.

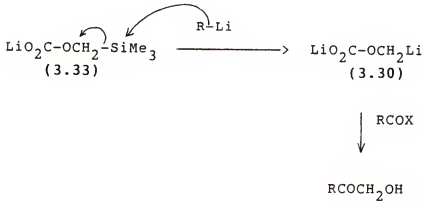
Table 3.1. Reaction of the α-Lithio Lithium Carbonate (3.34) with Electrophiles

	Electrophile	Product	Yield(%)
1.	p-Me-$C_6H_4CO_2Et$	p-Me-$C_6H_4COCH_2OH$	68
2.	PhCOCl	$PhCOCH_2OH$	23
3.	$PhCONMe_2$	$PhCOCH_2OH$	63
4.	PhCN	$PhCOCH_2OH$	65
5.	$PhCH=CHCO_2Et$	$PhCH=CHCOCH_2OH$	45
6.	$Me_2C=CHCO_2Et$	$Me_2C=CHCOCH_2OH$	60

All the hydroxymethyl ketones prepared in this study were characterized by their NMR spectra (^1H and ^{13}C) and through matching melting point data (in case of known compounds). The ^1H-NMR spectra of these compounds showed a characteristic two-proton singlet around 4.8 ppm which was assigned tc the methylene protons. Their ^{13}C-NMR spectra displayed the keto-carbonyl, usually near 198 ppm, whereas the methylene carbon appeared around 67 ppm.

Saturated aliphatic esters such as ethyl propionate or ethyl butyrate, however, failed to provide homogenuous products when used as electrophiles. Similar failure was also observed with other potential acylating agents like propionic anhydride and N,N-dimethylpropionamide. Dimethyl carbonate and phenyl isocyanate also failed to give the desired products.

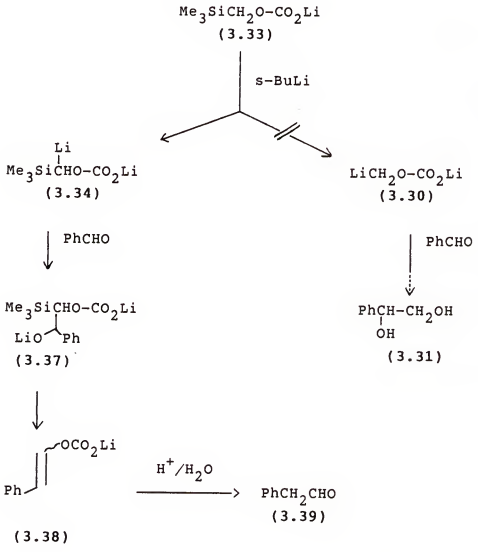
The results obtained thus far (Table 3.1) did not necessarily prove the formation of the α-lithio species **(3.34)**. There are reports that alkyllithiums attack the silicon center in certain Si-C bonds giving rise to the C-Li species [80MI4]. Such an attack on the lithium carbonate **(3.33)** could potentially give rise to the lithiomethyl lithium carbonate **(3.30)** (Scheme 3.12). The latter, upon reaction with esters, would afford the same results.



Scheme 3.12

The nature of the α-lithio species was decisively settled by using benzaldehyde as the electrophile. It was envisaged that reaction of benzaldehyde with the silyl-α-lithio species **(3.34)** would initially produce a β-hydroxysilyl adduct **(3.37)**. The latter, after Peterson olefination [84S384] and subsequent hydrolysis of the incipient styryl carbonate **(3.38)**, should lead to phenylacetaldehyde **(3.39)** (Scheme 3.13). On the other hand,

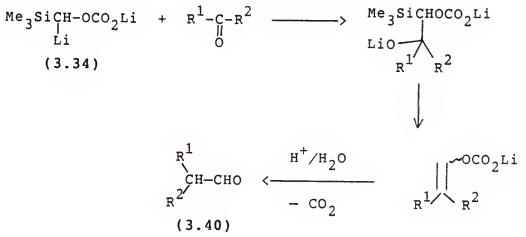
if α-lithiomethyl lithium carbonate (3.30) was indeed the reactive species, then its reaction with benzaldehyde would produce the diol (3.31).



Scheme 3.13

In practice, α-lithiation of the lithium carbonate **(3.33)** with s-butyllithium (-25°C, 2 hrs) followed by addition of benzaldehyde produced phenylacetaldehyde **(3.39)** in 70% yield, as the sole product. This proved that the silyl-α-lithio species **(3.34)** is indeed formed and no lithiodesilylation (to give **3.30**) had taken place. This also reinforced the earlier view that with the other carbonyl electrophiles α-silyl-α-hydroxy ketones are the initial products which protiodesilylate upon hydrolysis.

The fact that lithium α-lithiotrimethylsilylmethyl carbonate **(3.34)** converted benzaldehyde to phenylacetaldehyde immediately opens up a novel homologation process for aldehydes and ketones (Scheme 3.14). These transformations, although very common in multistep synthesis, suffer from the lack any general preparative method [76T1943]. The synthon **(3.34)** promised a one-pot procedure to achieve such transformations.



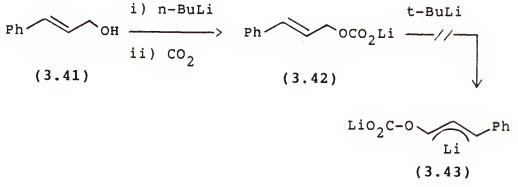
Scheme 3.14

In practice, reaction of the α-lithio species (3.34) with cyclohexanone resulted in a complex product mixture. Addition of $MgBr_2$ or $BF_3.Et_2O$ to the reaction mixture did not lead to the desired cyclohexane carboxaldehyde. In view of the enolization problems with cyclohexanone, benzophenone was next tried as the electrophile; however, the desired product could not be obtained. Further study with **3.34** as a reductive formyl anion equivalent was therefore abandoned.

At this time our attention was drawn to the recent fluoride induced desilylative alkylation of α-silylbenzyl alcohol [84CL1803]. However, no reaction was observed when benzaldehyde and the lithium carbonate **(3.33)** were together treated with $(Bu)_4N^+F^-$ (in tetrahydrofuran, 25°C, 24 hrs) or with CsF (in hexamethylphosphoramide, 60°C, 6 hrs). In another study, Sakurai has shown that one of the Si-C bonds in bis(trimethylsilyl)methane could be cleaved by sodium methoxide in hexamethylphosphoramide to produce the trimethylsilylmethyl carbanion [73TL4193]. A similar treatment of the lithium carbonate **(3.33)** was not fruitful and returned the starting materials. Generation of the methanol dianion equivalent directly from the lithium carbonate **(3.33)** was therefore deemed impossible.

3.2.3. α-Lithiation Studies on Lithium Cinnamyl Carbonate

Previous work in this group showed that allyl lithium carbonate could not be α-lithiated with t-butyllithium [86MI1]. Hence, a more activated system such as cinnamyl alcohol (3.41) was chosen for the present work. The required lithium cinnamyl carbonate (3.42) could be prepared very easily as shown in Scheme 3.15. The lithium carbonate (3.42) was next treated with t-butyllithium followed by addition of D_2O. Hydrolytic work-up followed by ^{1}H-NMR analysis of the product showed no deuterium incorporation in the molecule. This evidently showed that the desired allyl carbanion (3.43) could not be generated.



Scheme 3.15

Since other methods exist which allows for the generation of α-oxyallyl carbanions [84AG(E)932, 81AG(E)127], further investigation on the allyl hemicarbonates was discontinued.

3.3. Conclusions

The advantage of using carbon dioxide as a hydroxyl protecting group has been efficiently demonstrated. It is easily introduced and subsequent deprotection of the resultant hemicarbonates can be achieved under extremely mild conditions. The lithium carbonates are virtually inert to most metallating agents and the process of α-lithiation is devoid of the notorious 1,2-anionic migration. However, the lithium carbonates play no role in the process of α-activation. Presumably, the delocalized negative charge on the carbonate moiety reduces its co-ordinating power and the carbonyl oxygen fails to activate the lithiating agent (*via* the prior complexation mechanism [86ACR356]).

Lithium carbonates with appropriate α-activating auxilliaries promise very interesting synthetic transformations. As a result of the present investigation, lithium α-lithiotrimethylsilylmethyl carbonate (**3.34**) has emerged as a novel α-hydroxycarbanion synthon. In spite of its limitations, a novel synthesis of α-hydroxyketones has been developed by proper utilization of the synthon **3.34** and that too in a one-pot sequence starting from a commercially available material. α-Hydroxyketones are traditionally prepared *via* electrophilic hydroxylation of ketone enolates,

a procedure not without complications. Direct oxygenation often results in complex product mixtures due to over-oxidation [62J1578,68JOC3294,68JOC3695]. The MoO_5.Py.HMPA complex has also been used for this purpose but the products from methylketone enolates were found to undergo further condensation with the starting material, leading to poor yields [78JOC188]. However, Rubottom's m-CPBA oxidation of silyl enol ethers [78JOC1599] or Moriarty's method using hypervalent iodine oxidation [84TL691] are quite effective. By contrast, our route to hydroxymethyl ketones utilizes a novel sequence which is conceptually opposite to the existing ones and demonstrates the viability of an umpolung approach to these compounds.

3.4. Experimental

Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. NMR spectra were recorded on a Varian XL200 instrument using Me_4Si as the internal standard for protons and $CDCl_3$ (77.0 ppm) as reference for carbon resonances. The nature of the carbon signals in the ^{13}C-NMR spectra were determined by the

Attached Proton Test [81CC150, 82JMR535]. Mass spectra were recorded at 70 ev on a AEI MS instrument attached to a DS 55 database. All reactions were carried out in oven-dried (120°C, overnight) apparatus under a slight positive pressure of dry argon and transferring operations done using syringe techniques or via cannula. Tetrahydrofuran (THF) was freshly distilled from sodium-benzophenone ketyl just prior to use. Hexamethylphosphoramide (HMPA) and tetramethylethylenediamine (TMEDA) were distilled over CaH_2 under reduced pressure and stored under nitrogen. Flash chromatography [78JOC2923] was carried out over silica gel (MCB, 230-400 mesh) using pre-distilled solvents.

General Procedure for the Preparation and α-Alkylation of Lithium Trimethylsilylmethyl Carbonate (3.33):
A 250 ml Schlenk reactor (oven-dried at 120°C overnight) was evacuated under 0.5 mm for 2 hrs and purged with argon. 1-Trimethylsilylmethanol (3.32) (Aldrich or Petrarch) (0.52 g, 5.0 mmole) was added followed by dry THF (35 ml). After cooling to -78°C, n-BuLi (2.1 ml, 2.5 M in hexanes, 5.2 mmole) was added dropwise. The reactor was warmed to room temperature and held there for 10 min. It was then recooled

to -25°C and dry CO_2 gas bubbled through it. The cooling bath was removed and while CO_2 was still bubbled in, the reactor was allowed to warm to room temperature. After a further 5 min all volatile contents were evacuated at 0.5 mm leaving a white powdery residue of the lithium trimethylsilylmethyl carbonate **(3.33)**. The reactor was again purged with argon and dry THF (45 ml) was added to redissolve the white residue. After cooling to -78°C, s-BuLi (4.2 ml, 1.3 M in cyclohexane, 5.5 mmole) was added dropwise. Stirring was continued at -25°C for 2 h. To this virtually colorless solution was then added the appropriate electrophile (5.2 mmole) in dry THF (15 ml). The reactor was warmed to room temperature and the contents stirred for 30 min. The THF was removed under reduced pressure (on a rotary evaporator) and the residue treated with 10% aqueous HCl. After stirring for 15 min the aqueous phase was extracted with ether or ethyl acetate (3 X 15 ml). The combined organic layers were washed sequentially with water (10 ml), saturated $NaHCO_3$ solution (10 ml) and brine (10 ml) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the products which were purified as described for the individual cases below.

The following compounds were made according to the above procedure:

2-Hydroxy-(4'-methyl)phenylethanone

Ethyl p-toluate (0.82 g) was used as the electrophile. Silica gel chromatography using petroleum ether - 25% ethyl acetate afforded the product (0.50 g, 68%); m.p. 86-89°C (lit. [06CB3757] m.p. 89-90°C); δ_H ($CDCl_3$) 7.9 (2H, d, J 8 Hz), 7.4 (2H, d, J 8 Hz), 5.0 (2H, s), 3.5-3.2 (1H, broad) and 2.6 (3H, s); δ_C ($CDCl_3$) 197.9 (C=O), 145.3 (aryl CH), 130.8 (aryl CH), 129.6 (aryl C), 127.8 (aryl C), 65.2 (CH_2) and 21.8 (CH_3).

2-Hydroxyphenylethanone

(a) Benzoyl chloride (0.74 g) was used as the electrophile. Silica gel chromatography using petroleum ether - 20% ethyl acetate afforded the product (0.16 g, 23%); m.p.86-88°C (lit. [12LA(394)42] m.p. 89-90°C); δ_H 8.0-7.9 (2H, m), 7.7-7.5 (3H, m), 4.9 (2H, s) and 3.5-3.4 (1H, broad).

(b) N,N-Dimethylbenzamide (0.74 g) was used as the electrophile. Silica gel chromatography using petroleum ether - 20% ethyl acetate afforded the same product (0.42 g, 63%) identical in melting point and ^{1}H-NMR data to above.

(c) Benzonitrile (0.54 g) was used as electrophile. Silica gel chromatography using petroleum ether - 25% ethyl acetate afforded the same product (0.44 g, 65%) identical in melting point and ^{1}H-NMR data to above.

trans-1-Hydroxy-4-phenylbut-3-en-2-one

trans-Ethyl cinnamate (0.88 g) was used as the electrophile. Silica gel chromatography using petroleum ether - 20% ethyl acetate afforded the product (0.34 g, 42%); m.p. 65-68°C (lit. [84TL691] m.p. 69-70.5°C); δ_H ($CDCl_3$) 7.9-7.5 (6H, m), 6.8 (1H, d, J 15 Hz), 4.5 (2H, s) and 2.9 (broad, OH); δ_C ($CDCl_3$) 198.1 (C=O), 144.1, 133.4, 131.1, 129.0, 128.4, 121.0 and 67.0 (CH_2).

1-Hydroxy-4-methylpent-3-en-2-one

Ethyl 3,3-dimethylacrylate (0.64 g) was used as the electrophile. Silica gel chromatography using petroleum ether - 10% ethyl acetate afforded the product (0.34 g, 60%)

as an oil; δ_H ($CDCl_3$) 5.9 (1H, s), 4.2 (2H, s), 2.3 (broad, OH), 2.2 (3H, s) and 1.9 (3H, s); δ_C ($CDCl_3$) 198.0 (C=O), 158.9 (C-3), 119.0 (C-2), 68.6 (CH_2), 27.8 (CH_3) and 21.4 (CH_3); HRMS: $M^{+\cdot}$ found 114.0728, $C_6H_{10}O_2$ requires 114.0681.

Phenylacetaldehyde

Benzaldehyde (0.52 g) was used as the electrophile. Filtration through a short column of neutral alumina using hexane-2% ethyl acetate afforded the product (0.52 g, 78%); δ_H ($CDCl_3$) 9.74 (1H, t, J 2 Hz), 7.4-7.2 (5H, m) and 3.67 (2H, d, J 2 Hz).

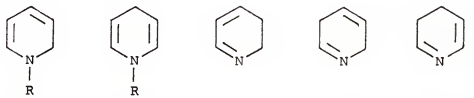
CHAPTER IV

THERMAL BEHAVIOR OF N-VINYL-1,2-DIHYDROPYRIDINES

4.1. Introduction

4.1.1. 1,2-Dihydropyridines

Of the five possible classes of dihydropyridine **(4.1-4.5)**, the 1,2- **(4.1)** and 1,4-dihydropyridines **(4.2)** have attracted most attention. The rest have been less studied because of their instability and the lack of good preparative methods.



(4.1) **(4.2)** **(4.3)** **(4.4)** **(4.5)**

The chemistry of dihydropyridines has been extensively reviewed [72CRV1,82CRV223,82MI1]. As compared to

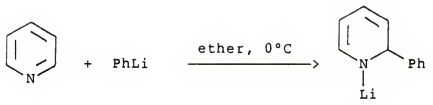
1,4-dihydropyridines, which have been widely exploited as NADH mimics, 1,2-dihydropyridines until recently, have found less prominence. This may be partly attributed to their lower stability [72JA5926]; 1,2-dihydropyridines are readily oxidized to the corresponding pyridines. In recent years, however, 1,2-dihydropyridines have found widespread use in natural product synthesis; these highly reactive compounds have proved to be important building blocks in the synthesis of various alkaloids, especially for the indoloquinolizidine [75ACS(B)655,76ACS(B)251,80TL2341], elaeocarpine [71TL4395] and cantharanthine [78TL5157,79TL2485,80JOC3382] families.

4.1.2. Synthetic Routes to 1,2-Dihydropyridines

Due to their inherent instability there are only few methods of preparing 1,2-dihydropyridines. These are described below.

4.1.2.1. Reaction of Nucleophiles with Pyridines

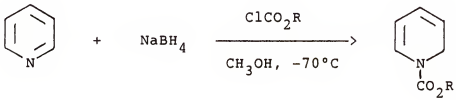
Strong nucleophiles such as phenyllithium add to pyridine exclusively at the 2-position to form the highly reactive N-lithio-1,2-dihydropyridine **(4.6)** [71TL4961]. This is currently the only practical way of synthesizing 1,2-dihydropyridines directly from pyridines (Scheme 4.1).



(4.6)

Scheme 4.1

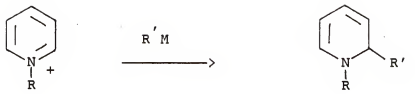
Normally pyridines (unless highly deactivated by electron withdrawing groups) are not reduced by sodium borohydride. However, in presence of alkyl chloroformates, sodium borohydride reduces the incipient pyridinium salt to give high yields of N-carbamoyl-1,2-dihydropyridines [72JOC1321] (Scheme 4.2). In an analogous manner, other nucleophiles such as Grignard reagents [82JOC4315,83TL1801, 84TL4867] and cyanide ion (to form Reissert compounds) [85CI(L)125] have also been successfully employed.



Scheme 4.2

4.1.2.2. Reaction of Nucleophiles with Pyridinium Salts

Pyridinium salts are more susceptible to nucleophilic attack than the corresponding pyridines. However, depending on the nucleophile, the regioselectivity of the attack (1,2- *vs.* 1,4-) varies and, quite often, mixtures of 1,2- and 1,4-dihydropyridines are obtained. This problem has been addressed with reference to the "hardness" or "softness" of the nucleophile [65TL4615] and there is evidence that in some cases a mixture of 1,2- and 1,4-isomers are formed under kinetic control which subsequently equilibrates to the thermodynamically more stable 1,4-isomer [79JOC1757]. Enhanced 1,2-regioselectivity is generally observed in the reaction of pyridinium salts with organometallic reagents. Thus Grignard reagents generally attack at the 2-position to form 1,2-dihydropyridines [74TL59,71JOC772] (Scheme 4.3). Good yields of 1,2-dihydropyridines are also obtained when phenyllithium or *t*-butyllithium is used [72CZ411,74JOC59] but simpler alkyllithiums tend to give very low yields. Organocuprates usually attack pyridinium salts at the 4-position [74CJC3563]. Nucleophilic attack on a 4-substituted pyridinium salt invariably occurs at the 2-position. One exception being benzylic organotin reagents, which, in the presence of chloroformates, always attack the 4-position of a pyridine, even when a 4-substituted pyridine is used [86TL211].



R'M = PhMgBr 70%
EtMgBr 70%
PhLi 80%
n-PrLi 20%

Scheme 4.3

Sodium borohydride reduction of pyridinium salts is difficult to arrest at the dihydropyridine stage and over-reduction to tetrahydropyridines usually occur[53BSF53, 70JOC2809,86AHC(39)1].

To summarize, the most synthetically useful methods for preparing 1,2-dihydropyridines are:

i) Reaction of pyridines with sodium borohydride in presence of chloroformates, or

ii) Reaction of pyridinium salts with Grignard reagents.

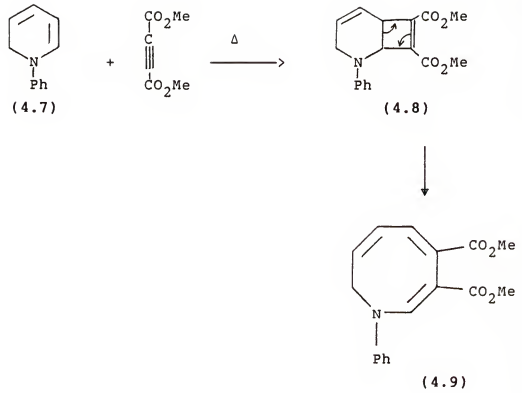
4.1.3. Reactivity of 1,2-Dihydropyridines

The reactivity of 1,2-dihydropyridines ranges from that of an enamine [75CJC2305,76JHC789,79JCS(PI)3082,75JOC569, 78CJC1026,79CJC2342,79JHC409] to that of a cyclic 1,3-diene.

4.1.3.1. Cycloaddition Reactions

Depending on the nature of the N-substituent, 1,2-dihydropyridines behave as either a 4π or a 2π component in cycloaddition reactions. When the N-substituent is an electron withdrawing group, 1,2-dihydropyridines behave as the 4π component in cycloaddition reactions. There are numerous reports of intermolecular Diels-Alder reactions where 1,2-dihydropyridines were effeciently used as the diene component [76JHC481,80JA6157,80CJC2447,81JOC4836, 82TL2527,83TL2927,85JOC3236,85TL2617]. The intramolecular version is also known [74HCA1204,83TL2711].

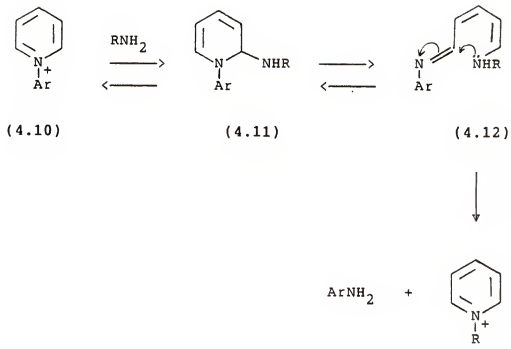
In absence of electron withdrawing N-substituents, 1,2-dihydropyridines behave more like enamines and hence undergo thermal [2+2] cycloadditions. An example of thermal [2+2] cycloaddition of 1,2-dihydropyridines is shown in Scheme 4.4. Thus 1-phenyl-1,2-dihydropyridine **(4.7)** on heating with dimethyl acetylenedicarboxylate gave rise to the 1,2-dihydroazocine derivative **(4.9)**. The formation of the latter was rationalized through an initial [2+2] adduct **(4.8)** which underwent further cycloreversion to produce the observed product [74JCS(PI)2496].



Scheme 4.4

4.1.3.2. Electrocyclic Reactions

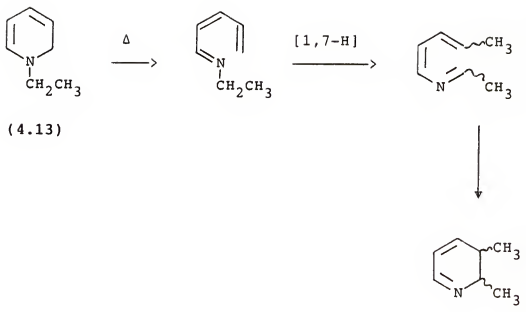
The ANRORC reaction (Addition of Nucleophile - Ring Opening - Ring Closure) is probably the most studied electrocyclic reaction involving 1,2-dihydropyridines. A crucial step in this reaction sequence is the electrocyclic ring opening of the intermediate 1,2-dihydropyridine **(4.11)** to the triene **(4.12)** (Scheme 4.5). A detailed mechanistic discussion can be found in the recent reviews on ANRORC-type reactions [80MI3,80S589,81T3423]. Similar ring openings of pyridine N-oxides are also known [67T2775,69T4291,71JOC1705, 74T4055,76TL4717].



Ar = 2,4-dinitrophenyl

Scheme 4.5

Thermally-induced electrocyclic reactions are very rare for 1,2-dihydropyridines. One such example is the thermal isomerization of 1-ethyl-1,2-dihydropyridine **(4.13)** to the 2,3-dihydropyridine derivative **(4.14)** (Scheme 4.6) [78JA6696]. The lack of many such examples probably reflects the greater thermodynamic stability of 1,2-dihydropyridines as compared to 1-azatrienes [80MI3].



(4.13)

(4.14)

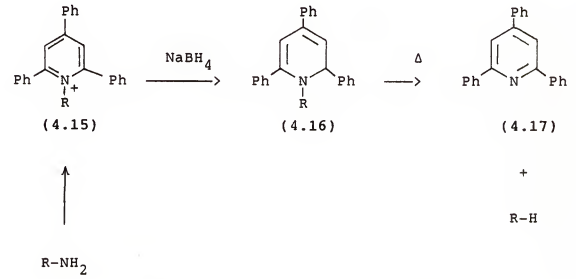
Scheme 4.6

4.1.4. Effects of N-Substituents on the Thermal Behavior of 1,2-Dihydropyridnes

4.1.4.1. N-Alkyl and N-Aryl Substituents

N-Aryl-1,2-dihydropyridines are more stable under pyrolytic conditions than the corresponding N-alkyl derivatives [79JCS(PI)442]. The latter, on pyrolysis, yield the parent pyridine together with the hydrocarbon derived from the N-substituent. This has been effectively exploited

by Katritzky and co-workers for the three-step reductive deamination of primary amines [84JCS(PI)1671] (Scheme 4.7). Although usually limited to allyl, benzyl or heterobenzyl amines, in some cases, it can be extended to alkyl amines.



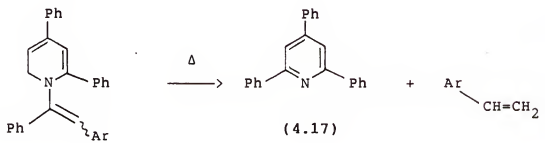
R = allyl, benzyl or heterobenzyl

Scheme 4.7

4.1.4.2. N-Vinyl Substituents

In a manner similar to the N-alkyl-1,2-dihydropyridines, pyrolysis of a N-vinyl-1,2-dihydropyridine might be expected to yield an olefin corresponding to the N-vinyl substituent; however, this was not the case. When the dihydropyridine **(4.18)** was pyrolyzed for 2 hrs (180°C, 0.1 mm),

m-chlorostyrene and 2,4,6-triphenylpyridine (**4.17**) were formed [82JOC492] (Scheme 4.8).

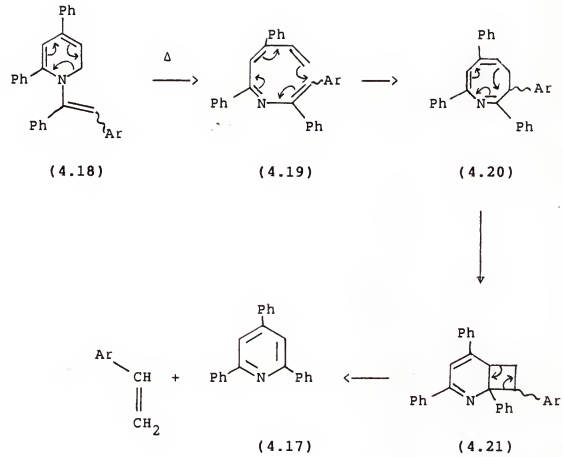


(**4.18**) (**4.17**)

Ar = 3-chlorophenyl

Scheme 4.8

Apparently the result of a rearrangement, the above transformation was rationalized as shown in Scheme 4.9. After initial electrocyclic ring opening of the 1,2-dihydropyridine (**4.18**), the resultant 3-azatetraene (**4.19**) could lead to the bicyclic intermediate (**4.21**) via two consecutive electrocyclizations. The intermediate (**4.21**) underwent fragmentation and consequent aromatization to afford the observed products. Pyrolysis of some other N-styryl-1,2-dihydropyridines followed the same fragmentation pattern [82JOC492].



(4.18) (4.19) (4.20)

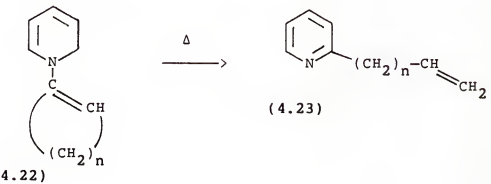
(4.17) (4.21)

Scheme 4.9

4.1.5. Aims of the work

As discussed above, pyrolysis of N-vinyl-1,2-dihydropyridines led to an interesting fragmentative rearrangement. The aim of the present project was to extend this observation to 1,2-dihydropyridines having an N-cycloalkenyl substituent. Thus the latter class

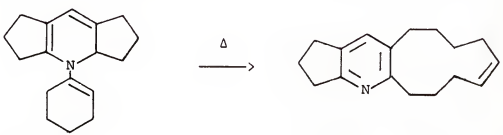
of dihydropyridines (e.g. **4.22**), on pyrolysis, would be expected to give pyridines **4.23**, having long side chains (Scheme 4.10).



(4.22) **(4.23)**

Scheme 4.10

As a further extension, by capping the dihydropyridine nucleus with cycloalkyl groups as in **4.24**, medium-ring fused pyridines such as **4.25** might be obtained (Scheme 4.11).



(4.24) **(4.25)**

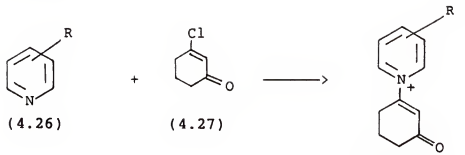
Scheme 4.11

4.2. Results and Discussion

4.2.1. Synthetic Strategy

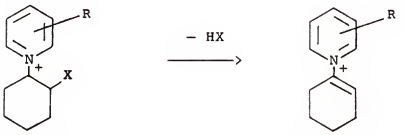
We intended to prepare the required N-cycloalkenyl-1,2-dihydropyridines by sodium borohydride reduction of the corresponding pyridinium salts. Thus our primary synthetic targets were the N-cycloalkenylpyridinium salts. At the time of this work, no such N-vinylpyridinium salts were known where the vinyl grouping was part of a carbocycle. Our strategy for the preparation of such salts comprised of two basic pathways as illustrated in Scheme 4.12. In Path A, it was envisioned that a suitable pyridine (**4.26**) would displace the halogen from β-chlorocycloalkenones (**4.27**), thus leading to N-cycloalkenonylpyridinium salts (**4.28**). Path B, on the other hand, requires the preformation of a suitable pyridinium salt (**4.29**) with a β-substituted cycloalkyl group as the N-substituent. The latter, on elimination of HX, might afford the desired N-cycloalkenylpyridinium salts (**4.30**). The latter pathway is quite similar to the one generally followed for the preparation of acyclic N-vinylpyridinium salts [83JOC4017].

Path A:



(4.26) (4.27) (4.28)

Path B:



(4.29) (4.30)

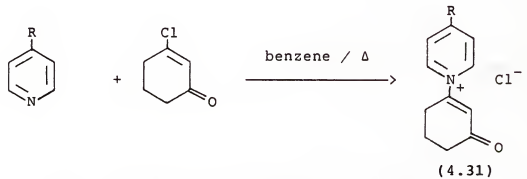
X = Cl, Br, OH

Scheme 4.12

4.2.2. Preparation of N-(Cycloalken-3-on-1-yl)pyridinium Salts

To test the viability of Path A in Scheme 4.12, the reaction of pyridine and β-chlorocyclohexenone [76JOC636] was attempted. The reaction was monitored by ^{1}H-NMR ($CDCl_3$, 55°C) and was found to be quite slow. It was only after

48 hrs that the α-protons of the pyridinium salt (4.31a) appeared in the spectrum (at ~ 10.1 ppm). However, with more nucleophilic pyridines such as p-dimethylaminopyridine (DMAP) the reaction was much faster and the derived pyridinium salt (4.31b) could be isolated in very good yield (94%) (Scheme 4.13). 4-Phenylpyridine could also be used which gave the corresponding pyridinium salt (4.31c) in 57% yield; 4-picoline, however, gave an intractable product mixture. In these reactions, the best yields were obtained when benzene was used as the solvent; in chloroform or acetonitrile the yields were much lower.



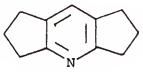
(4.31)

a, R = H; b, R = NMe_2; c, R = Ph

Scheme 4.13

When the tricyclic pyridine (4.32) [71JPS(A-I)(9)1807] was reacted with β-chlorocyclohexenone, the reaction resulted in a complete failure, even when the components were heated in a sealed tube at 200°C for 24 hrs; starting

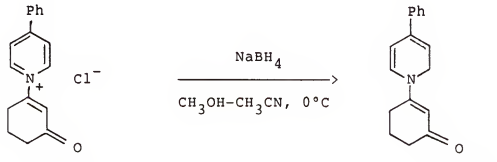
materials were recovered in each case. Steric inhibition on the part of the pyridine (**4.32**) was thought to be responsible for this failure.



(4.32)

4.2.3. Preparation of N-(Cycloalken-3-on-1-yl)-1,2-dihydropyridines

To prepare the N-cycloalkenonyl-1,2-dihydropyridines, the pyridinium salts **4.31b** and **4.31c** were subjected to sodium borohydride reduction. The salt **4.31b** showed a high degree of resistance toward borohydride reduction, even in refluxing methanol, presumably due to the strong electron-releasing effect of the p-dimethylamino group. On the other hand, the p-phenylpyridinium salt **4.31c** was smoothly reduced to the corresponding 1,2-dihydropyridine (**4.33**) in excellent yield (91%) (Scheme 4.14).

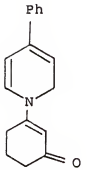


(4.31c) (4.33)

Scheme 4.14

The structure of 4.33 was confirmed by its ^{1}H and ^{13}C-NMR spectra. The ^{1}H-NMR chemical shifts of 4.33 are shown in Table 4.1. The two H-2 hydrogens showed the expected doublet (J = 4 Hz) at δ 4.4. The H-6 hydrogen appeared as a more downfield doublet (J = 8 Hz) at δ 6.6 whereas the H-3 and H-5 hydrogens formed a complex multiplet at δ 5.4-5.8. These chemical shifts and the multiplicities are in good accord with the characteristic pattern found in the reported ^{1}H-NMR spectra of 1,2-dihydropyridines [72CRV1]. In addition, the one-proton singlet at δ 5.3 was assigned to the vinyl proton of the N-cyclohexenone substituent.

The ^{13}C-NMR spectrum of the dihydropyridine 4.33 showed the carbonyl carbon at 197.0 ppm and three downfield methine signals at δ 114.6, 104.7 and 102.9 which were assigned to C-3, C-5 and the C-2' carbons, respectively. These assignments are only tentative and for C-5 and C-2' they may be interchanged. However, the C-2 methylene carbon could be assigned with certainity, being the most deshielded aliphatic signal at 47.3 ppm. The three remaining cyclohexenone carbons appeared at 36.0, 25.9 and 21.9 ppm.



(4.33)

Table 4.1 ^{1}H-NMR Data for Dihydropyridine (4.33)[a]

Chemical Shift Values					
N-Substituent		Dihydropyridine Ring			Phenyl
Vinyl	Others	2	3 & 5	6	Ring
5.3(s)[b]	1.8-2.5(m)	4.4(d)[c]	5.4-5.8(m)	6.6(d)[d]	7.4-7.6(m)

[a] chemical shifts in ppm downfield from Me_4Si.

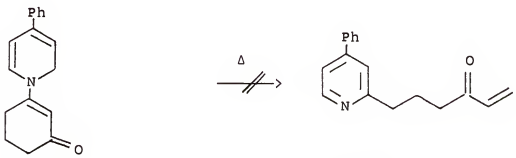
[b] multiplicities are given in parentheses : s = singlet, d = doublet, m = unresolved multiplet.

[c] J = 4 Hz.

[d] J = 8 Hz.

4.2.4. Pyrolysis of N-(Cycloalken-3-on-1-yl)-4-phenyl-1,2-dihydropyridine

As described above, pyrolysis of N-cycloalkenyl-1,2-dihydropyridines was our main objective. We embarked upon this objective with the dihydropyridine **4.33** in hand. According to the mechanism illustrated in Scheme 4.10, it was expected that the pyridine derivative **4.34** would result from the pyrolysis of **4.33** (Scheme 4.15).

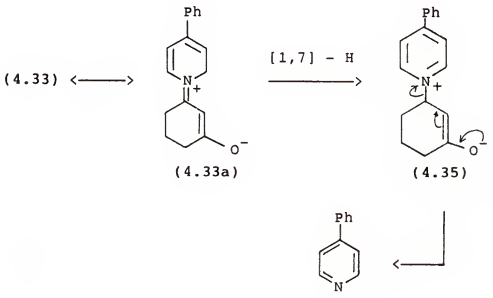


(4.33) **(4.34)**

Scheme 4.15

In practice, the pyrolysis of **4.33** was conducted in a Kugelrohr apparatus at 180°C at 0.1 mm pressure. After 6 hrs, a white crystalline sublimate was collected. The ^{1}H-NMR analysis of this solid showed no aliphatic hydrogens and indicated it to be 4-phenylpyridine. Elemental analysis and melting point data further confirmed this contention. However, the yield was a modest 25%. One possible mechanistic explanation is that in the canonical form 4.33a,

the dihydropyridine might have induced a 1,7-hydride shift to form the pyridinium zwitterion intermediate **4.35**, which then underwent a reverse-Michael process to eliminate 4-phenylpyridine (Scheme 4.16).



Scheme 4.16

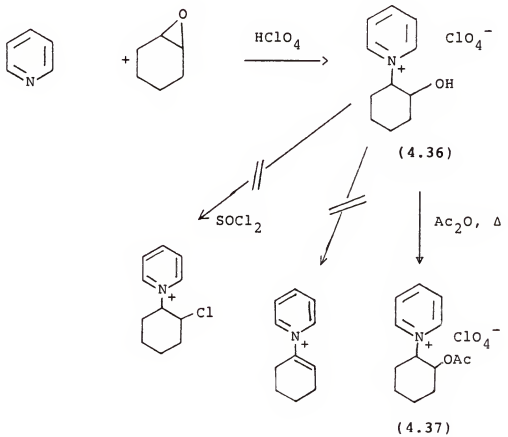
Partial support for this reasoning came from the mass spectral fragmentation data of **4.33** (M^+ = 251). The M^+-1 fragment ion at m/e 250 (65%) indicates facile oxidation to the pyridinium cation through the loss of a hydrogen. Further degradation to the 4-phenylpyridine fragment (m/e 155, base peak) was also observed together with the protonated form of 4-phenylpyridine (m/e 156, 40%). However, the cyclohexenonyl fragment (m/e 95) showed only a 4% intensity.

The vulnerability toward oxidation to the pyridinium cation shown by the dihydropyridine **4.33** would certainly be expected to discourage electrocyclic ring-opening of the dihydropyridine ring. Thus it became essential at this point to assess the role of the keto-function of **4.33** in its pyrolytic behavior. It was thought that the absence of such an electron sink would minimize the delocalization of the nitrogen lone pair and thus stabilize the dihydropyridine against oxidation and further fragmentation. This might allow sufficient lifetime for the electrocyclic ring-opening to occur. To test this hypothesis, we needed to prepare a 1,2-dihydropyridine with a simple N-cycloalkenyl substituent.

4.2.5. Preparation of N-(Cycloalken-1-yl)pyridinium Salts

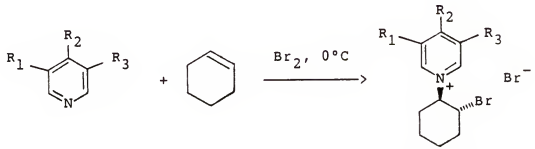
A general outline for the preparation of N-cycloalken-1-ylpyridinium salts was shown before as Path B in Scheme 4.12. This required the preformation of N-cyclohexylpyridinium salts suitably substituted with a leaving group at the β-position of the cyclohexyl ring. We thus started with the known [56JA2527] N-(β-hydroxycyclohexyl)pyridinium perchlorate **(4.36)** which was readily prepared by the addition of pyridine to

cyclohexene oxide in the presence of perchloric acid (Scheme 4.17). However, the hydroxyl group in **4.36** showed some unusual resistance towards thionyl chloride [83JOC4017] in attempts to convert it to the chloride. Dehydration of **4.36** with perchloric acid, p-toluenesulfonic acid (refluxing toluene with azeotropic removal of water) or with methyltriphenoxyphosphonium iodide [72JOC4190,84JCS(PI)1933] also failed. When the dehydration was attempted in boiling acetic anhydride, only the corresponding acetate **(4.37)** was obtained.



Scheme 4.17

Since the hydroxy group of **4.36** could not be transformed to the chloride, we resolved to prepare β-bromocyclohexylpyridinium salts, taking advantage of the fact that bromination of cyclohexene in presence of excess pyridine affords β-bromocyclohexylpyridinium bromide [50JA4524]. Although the yield of this reaction was reportedly low (20-40%), the ready availability of pyridines and the convenience of large scale preparation made it an attractive alternative. Thus, following this procedure, the novel pyridinium salts (**4.38b-c**) were easily prepared in yields ranging from 21 to 47% (Scheme 4.18). The stereochemistry of cyclohexane ring-substituents in **4.38** were tentatively assigned as "trans" [50JA4524].

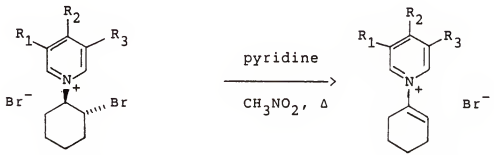


(4.38)

a; $R_1 = R_3 = H$, $R_2 = CH_3$
b; $R_1 = R_3 = CH_3$, $R_2 = H$
c; $R_1 = R_3 = H$, $R_2 = Ph$

Scheme 4.18

After an initial failure to dehydrobrominate the pyridinium salts **(4.38)** with NaOH [83JOC4017], it was found that treament with pyridine in refluxing nitromethane effects the dehydrobromination to yield the N-cyclohexenylpyridinium salts **(4.39)** (Scheme 4.19). Rather harsh conditions were necessary as the α-hydrogen and the β-bromine in the salts **4.38** are "syn" to each other and elimination via an E_2 transition state would be disfavored. We believe that, here the elimination of HBr proceeded through an E_1CB mechanism.



(4.38) **(4.39)**

a; $R_1 = R_3 = H$, $R_2 = CH_3$
b; $R_1 = R_3 = CH_3$, $R_2 = H$
c; $R_1 = R_3 = H$, $R_2 = Ph$

Scheme 4.19

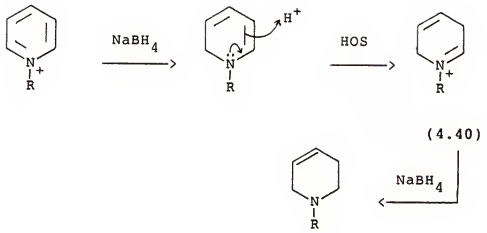
Formation of the N-cyclohexenyl linkage was supported by the ^{1}H-NMR spectra of the salts **4.39**. Each of these salts showed a characteristic one-proton multiplet around δ 6.6,

which was assigned to the vinyl proton of the cyclohexene ring. The set of multiplets at δ 4.8-5.2, characteristic of the α and β protons of the cyclohexyl ring of the starting pyridinium salts (**4.38**), disappeared. The N-vinyl salts (**4.39a** and **4.39b**) were highly hygroscopic. Anion exchange to the more stable tetrafluroborate (with HBF_4, $AgBF_4$, $NaBF_4$) or to the perchlorate (with $NaClO_4$) was unsuccessful. The bromide **4.39c** was comparatively stable and easier to handle.

The dicyclopentanoid pyridine (**4.32**) failed again to react with cyclohexene oxide or with cyclohexene-bromine mixture in the desired fashion. Further investigations toward a N-cycloalkenylpyridinium salt incorporating a tricyclic pyridine skeleton was thus abandoned.

4.2.6. Preparation of N-(Cycloalken-1-yl)-1,2-dihydropyridines

It is very well documented that borohydride reductions of pyridinium salts are usually accompanied by overreduction to the tetrahydropyridines [86AHC(39)1]. This evidently occurs *via* the formation of an intermediate iminium salt (**4.40**) which is produced by the uptake of a proton (from the solvent) by the incipient 1,2-dihydropyridine (Scheme 4.20).

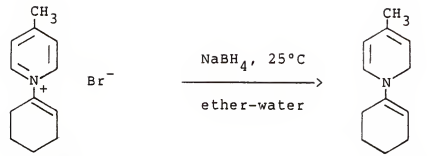


Scheme 4.20

Apart from the problem of overreduction, the question regarding the 1,2- *vs.* 1,4-attack of the hydride on the pyridinium ring needs to be adressed, also. By selecting a 4-picoline moiety, as in **4.39a**, the hydride attack could be directed exclusively at the 2-position; the same argument holds true for the 4-phenylpyridinium salt **4.39c**. The 3,5-lutidine system (**4.39b**) was chosen so that, in the corresponding 1,2-dihydropyridine, the methyl groups would offer some resistance towards protonation of the enamine system. Thus, formation of an iminium ion (*cf.* **4.40**) would be retarded, as would be further reduction. To test these

hypotheses and arrive at an optimum system, sodium borohydride reduction of the salts **4.39**(a-c) was undertaken. An extensive survey of the literature also revealed that certain experimental conditions, when properly adopted, can minimize the problem of over-reduction. The method chosen for this study was the "biphasic" reduction mode developed by Kutney and co-workers [77H593]. By this method, the reduction is carried out in a biphasic mixture of benzene and aqueous alkali. Once the dihydropyridines were formed they were immediately extracted into the organic phase, thus minimizing further reduction.

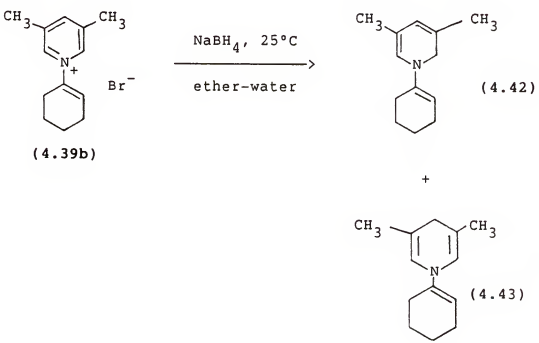
When the pyridinium salts (**4.39**a-c) were reduced with one equivalent of $NaBH_4$ under a biphasic condition [H_2O(pH 10)-ether], the preferential formation of the 1,2-dihydropyridines was observed. The ^{1}H-NMR spectrum of the crude product derived from **4.39**a showed characteristic peaks for the 1,2-dihydropyridine (**4.41**) (Scheme 4.21). It showed a 1H doublet (J = 6 Hz) at δ 6.5 (for H-6), a 1H multiplet at δ 5.1 (cyclohexene sp^2 hydrogen) and a narrow 2H doublet (J = 4 Hz) at δ 4.2 (for H-2). The H-3 and H-5 hydrogens of the dihydropyridine ring formed a multiplet at δ 4.7-5.0 while the saturated hydrogens of the cyclohexene ring clustered at δ 1.5-2.5.



(4.39a) (4.41)

Scheme 4.21

Under similar reaction conditions, the pyridinium salt **4.39b** was also reduced, but gave a mixture of 1,2- and 1,4-dihydropyridines (**4.42** and **4.43**) (Scheme 4.22).

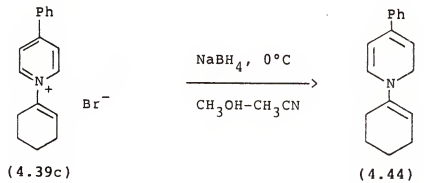


(4.39b)

Scheme 4.22

The ^{1}H-NMR of the reaction product from **4.39b** showed one-proton singlets at δ 6.3 and 4.5, a 1H multiplet at δ 5.7 together with a 2H singlet at δ 4.0. These signals were assigned to the 1,2-dihydropyridine (**4.42**). Also present were a singlet at δ 6.1 (2H), a multiplet at δ 5.1 (1H) and another singlet at δ 2.8 (2H). These latter peaks indicated the presence of the 1,4-dihydropyridine (**4.43**). From the spectral integral, the ratio of **4.42** to **4.43** was found to be 6 : 1. However, these dihydropyridines (**4.41-4.43**) were extremely unstable and attempts at their purification (flash chromatography, neutral alumina) met with failures.

On the other hand, the 4-phenylpyridinium salt **4.39c** was reduced by sodium borohydride to give a more stable 1,2-dihydropyridine (**4.44**) (Scheme 4.23). In this case, the reaction did not require the "biphasic" conditions and may be carried out in methanol-acetonitrile mixture at 0°C; the dihydropyridine (**4.44**), once formed, precipitated out of the medium and thus escaped further reduction.



(**4.39c**) (**4.44**)

Scheme 4.23

The structure of the dihydropyridine **4.44** was confirmed by its ^{1}H and ^{13}C-NMR spectra. The ^{1}H-NMR spectrum of **4.44** is illustrated in Figure 4.1. The one proton doublet (J = 8 Hz) at δ 6.5 is due to the H-6 hydrogen whereas the complex multiplet at δ 5.5 was assigned to the H-3 hydrogen. The H-5 proton gave rise to the doublet of doublets (ABX pattern) at 5.1 ppm: the higher coupling (J = 8 Hz) is due to the H-6 hydrogen while H-3 splits the H-5 proton with a smaller coupling constant (J = 2 Hz). The remaining doublet (J = 4 Hz) at δ 4.3 was assigned to the two H-2 protons and the multiplet at δ 4.6 to the vinyl proton of the N-cyclohexenyl ring.

The ^{13}C-NMR spectrum of **4.44** is shown in Figure 4.2A. Five relatively upfield resonances were observed, of which the most downfield signal at δ 46.8 was assigned to the C-2 of the 1,2-dihydropyridine nucleus. Figure 4.2B shows the ^{13}C-NMR spectra of the same dihydropyridine **(4.44)** run under the APT (Attached Proton Test) pulse sequence [81CC150, 82JMR535]. The peaks above the baseline signify the CH_2 and the quarternary carbons while those below are due to the CH_3's and CH's. Assignments of the dihydropyridine ring-carbons was difficult, not only due to lack of model spectra but also because of the overlapping signals from the 4-phenyl group. However, the spectra can clearly account for the requisite number of carbons present in **4.44**.

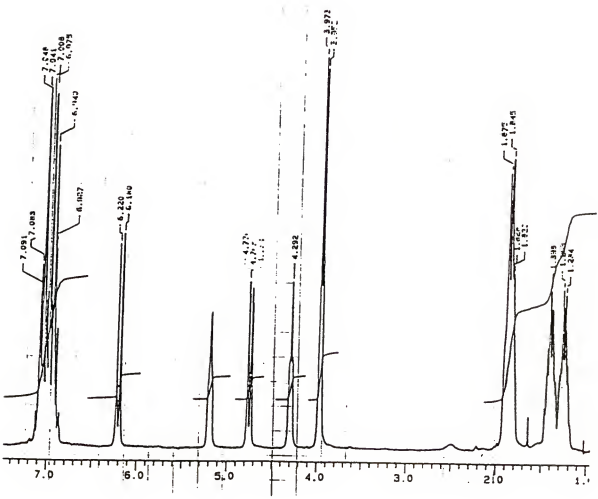


Figure 4.1. ^{1}H-NMR Spectrum of the 1,2-Dihydropyridine 4.44.

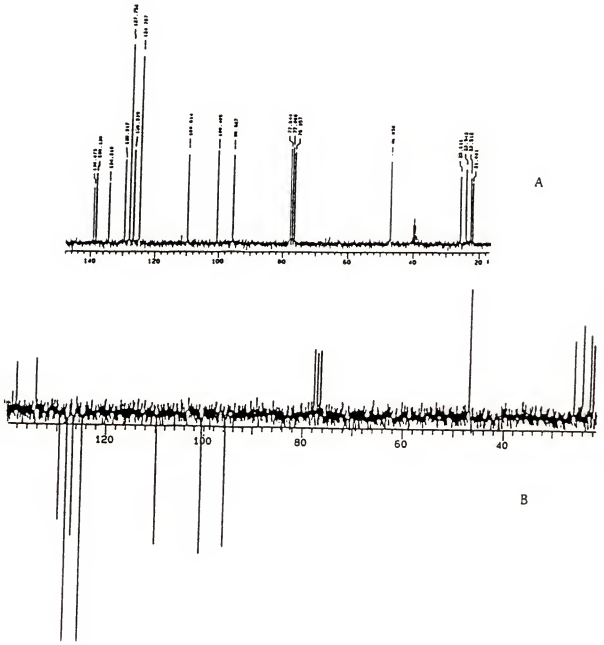


Figure 4.2. Proton Decoupled ^{13}C-NMR Spectra of the 1,2-Dihydropyridine 4.44.
A) Normal Spectrum B) Under APT Mode

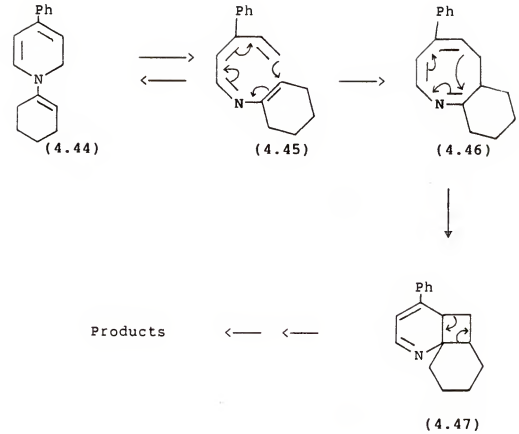
4.2.7. Pyrolysis of N-(Cycloalken-1-yl)-4-phenyl-1,2-dihydropyridine

Pyrolysis of the more stable dihydropyridine (**4.44**) was carried out at 180°C under 0.1 mm. After 4 hrs a white crystalline sublimate was collected. Unfortunately, it again turned out to be 4-phenylpyridine (matching NMR and melting point data),albeit in low yield (20%).

The mass spectral fragmentation pattern for **4.44** is supportive of radical fragmentation. Initial loss of hydrogen gives rise to the pyridinium fragment (m/e 236) which constitutes the base peak. Other prominent peaks are at m/e 156 (16%) and 155 (14%) from the protonated 4-phenylpyridine and free base fragments, respectively.

4.3. Conclusions

The thermolytic rearrangement shown by acyclic N-vinyl-1,2-dihydropyridines could not be extended to their cyclic counterparts. Considering that cyclic N-vinyldihydropyridines should obey the same ring opening-ring contraction sequence as proposed for the acyclic ones, the following set of transformations (Scheme 4.24) should hold true for **4.44**.



Scheme 4.24

In Scheme 4.24, the intermediate **4.47** appears to have a highly strained sp^3 carbon. Thus, even if the tetraene **4.45** is formed, it probably reverts back to the dihydropyridine, only to be oxidized to the corresponding pyridine. In fact, the mass spectra of the dihydropyridines (**4.33**) and (**4.44**) provided strong indications for this. Unfortunately, the mass spectral fragmentation of the acyclic 1,2-dihydropyridines (**4.18**) were not available for direct comparision.

4.4. Experimental

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^{1}H-NMR spectra were recorded either on a Varian EM 360L (60 MHz) or a Varian XL-200 (200 MHz) instrument. Chemical shifts are reported in δ (ppm) values downfield from Me_4Si unless specified otherwise. ^{13}C-NMR spectra were taken either on a JEOL FX-100 (25 MHz) or a Varian XL-200 (50 MHz) spectrometer with $CDCl_3$ (77.0 ppm) or $(CD_3)_2SO$ (39.5 ppm) as reference. IR spectra were recorded on a Perkin Elmer 283B instrument. Mass spectra were obtained at 70 ev on a AEI MS 30 mass spectrometer connected to a DS 55 data system. Elemental analyses (C, H, N, F) were carried out by Dr. R. W. King of this department. Removal of solvent under reduced pressure refers to solvent evaporation on a rotary evaporator connected to a water aspirator. All solvents were distilled over appropriate drying agents under nitrogen prior to use.

The following compounds were prepared according to the known literature procedures: 3-Chlorocyclohex-2-ene-1-one, b.p. 62-63°C/4 mm (lit. [76JOC636] b.p. 63°C/4 mm); 1,2,3,5,6,7-Hexahydrodicyclopentanoid[b,e]pyridine (4.32), m.p. 85-87°C (lit. [71JPS(A-I)(9)1807] m.p. 87°C); 1-(2-Hydroxycyclohexyl)pyridinium perchlorate (4.36), m.p. 118-119°C (lit. [56JA2527] m.p. 122°C);

1-[3-(Cyclohex-2-ene-1-on)-yl]-4-dimethylaminopyridinium chloride (4.31b).

4-Dimethylaminopyridine (0.94 g, 7.7 mmole) and β-chlorocyclohexenone (1 g, 7 mmole) in dry benzene (10 ml) was heated under reflux for 2 hrs. The precipitate formed was filtered, washed with ether and dried. Recrystallization from ethanol-ether gave the pyridinium chloride (4.31b) as white microcrystals (1.7 g, 94%), m.p. 120-122°C (Found: C, 61.60, H, 6.90, N, 11.42. $C_{13}H_{17}ClN_2O$ requires C, 61.77, H, 6.78, N, 11.08%); δ_H (D_2O, DSS as internal standard) 8.5 (2H, d, J 7 Hz), 7.2 (2H, d, J 7 Hz), 6.5 (1H, s), 3.5 (6H, s), and 3.2-2.2 (6H, m).

1-[(Cyclohex-2-ene-1-on)-3-yl]-4-phenylpyridinium chloride (4.31c).

4-Phenylpyridine (4.7 g, 30 mmole) and β-chlorocyclohexenone (4 g, 30 mmole) in dry benzene (25 ml) was heated under reflux for 36 hrs. The precipitate formed was filtered, washed with ether and dried (4.8 g, 57%), m.p. 191-192°C. δ_H (DMSO-d_6) 9.2 (2H, d, J 7 Hz), 8.5 (2H, d, J 7 Hz) 8.2-7.6 (5H, m), 6.7 (1H, s), 3.3-3.2 (2H, m), and 3.0-2.3 (4H, m). For analytical purpose, the tetrafluoroborate salt (prepared by anion exchange with a slight excess of sodium tetrafluoroborate in water) was used. Recrystallized

from ethanol as needles, m.p. 223-225°C (Found: C, 60.82, H, 4.62, N, 4.02. $C_{17}H_{16}BF_4NO$ requires C, 60.56, H, 4.78, N, 4.15%).

1-[(Cyclohex-2-ene-1-on)-3-yl]-4-phenyl-1,2-dihydropyridine (4.33).

1-[(cyclohex-2-ene-1-on)-3-yl]-4-phenylpyridinium chloride (4.31c) (2 g, 7 mmole) dissolved in acetonitrile-methanol (2:1, 25 ml) was cooled to 0°C. Sodium borohydride (0.27 g, 7 mmole) in water (5 ml) made alkaline (pH 10) with 10% sodium hydroxide was added dropwise and the mixture stirred for 2 hrs. Water (50 ml) was then added to give a yellow precipitate which was washed with cold water (2 X 10 ml) and dried under vacuum over phosphorus pentoxide (1.7 g, 91%); m.p. 135-139°C; HRMS: $\underline{M}^{+\cdot}$ found, 251.1287. $C_{17}H_{17}NO$ requires 251.1310 a.m.u.; δ_H ($CDCl_3$) 7.6-7.4 (5H, m) 6.6 (1H, d, $\underline{J}$ 8 Hz), 5.8-5.4 (2H, m), 5.3 (1H, s), 4.4 (2H, d, $\underline{J}$ 4 Hz), and 2.5-1.8 (6H, m); δ_C ($CDCl_3$) 197.0 ($\underline{C}$=O), 158.9, 137.9, 132.9, 128.4, 127.6, 126.7, 125.0, 114.6 ($\underline{C}$-3), 104.7 ($\underline{C}$-5), 102.9 ($\underline{C}$-2'), 47.3 ($\underline{C}$-2), 36.0, 25.9, and 21.9.

Pyrolysis of 1-[(Cyclohex-2-ene-1-on)-3-yl]-4-phenyl-1,2-dihydropyridine (4.33).

The 1,2-dihydropyridine (4.33) (0.5 g, 2 mmole) was heated for 6 hrs at 180°C under 0.1 mm of Hg in a Kughelrohr

apparatus. The white sublimate formed proved to be 4-phenylpyridine (0.08 g, 25%); m.p. 68-70°C (lit., m.p. 69-70°C); δ_H ($CDCl_3$) 8.8 (2H, d, J 8 Hz) and 7.8-7.4 (7H, m).

N-(2-Acetoxycyclohexyl)pyridinium perchlorate (4.37).

N-(2-Hydroxycyclohexyl)pyridinium perchlorate (4.36) (2.0 g, 7.2 mmole) in acetic anhydride (10 ml) was heated under reflux for 24 hrs. After cooling the solution to room temperature, acetone (20 ml) was added and the whole was added dropwise to dry ether (100 ml). The precipitate which formed was filtered, washed with ether and was recrystallized from ethanol (2.3 g, 98%); m.p. 198-200°C (Found C, 48.83, H, 5.72, N, 4.20. $C_{13}H_{18}ClNO_6$ requires C, 48.83, H, 5.67, N, 4.38%); δ_H (DMSO-d_6) 9.3 (2H, d, J 8 Hz), 9.0-8.6 (1H, m), 8.5-8.2 (1H, m), 5.5-4.6 (2H, m) and 2.5-1.2 (11H, m).

General Method for the Preparation of N-(2-Bromocyclohexyl) Pyridinium Salts (4.38).

Bromine (9.65 g, 60 mmole) was added dropwise to an ice cold mixture of cyclohexene (5.0 g, 60 mmole) and the appropriate pyridine (250 mmole) (in 25 ml of $CHCl_3$ when 4-phenylpyridine was used) over a period of 30 min. After stirring at room temperature for a further 30 min the

reaction mixture was triturated with ether (200 ml). The precipitate formed was filtered, washed with ether (2 X 25 ml), dried and crystallized from acetone-methanol to give white needles. The following pyridinium salts were made by this procedure:

1-(2-Bromocyclohexyl)-4-methylpyridinium Bromide (4.38a).

4-Methylpyridine was used as the pyridine component. Yield : 7.8 g (40%); m.p. 190-192°C (Found: C, 42.70, H, 5.02, N, 4.04. $C_{12}H_{17}Br_2N$ requires C, 43.01, H, 5.11, N, 4.18%); δ_H (DMSO-d_6) 9.2 (2H, d, J 8 Hz), 8.3 (2H, d, J 8 Hz) 5.1-4.8 (2H, m), 2.9 (3H, s) and 2.8-1.5 (8H, m).

1-(2-Bromocyclohexyl)-3,5-dimethylpyridinium Bromide (4.38b).

3,5-Dimethylpyridine was used as the pyridine component. Yield : 7.6 g (37%); m.p. 186-188°C (Found: C, 44.50, H, 5.46, N, 3.85. $C_{13}H_{19}Br_2N$ requires C, 44.72, H, 5.48, N, 4.01%); δ_H (D_2O, DSS as internal standard) 9.1 (2H, s), 8.7 (1H, s), 5.2-4.9 (2H, m) and 2.8-1.6 (14H, m).

1-(2-Bromocyclohexyl)-4-phenylpyridinium Bromide (4.38c).

4-Phenylpyridine was used as the pyridine component. Yield : 5.0 g (21%); m.p. 209-211°C (Found: C, 51.34, H, 4.85, N, 3.39. $C_{17}H_{19}Br_2N$ requires C, 51.41, H, 4.82, N,

3.52%); δ_H (DMSO-d_6) 9.6 (2H, d, J 8 Hz), 8.9 (2H, d, J 8 Hz), 8.6-8.3 (2H, m), 8.0-7.7 (3H, m), 5.4-5.1 (2H, m) and 2.8-1.6 (8H, m).

General Procedure for the Preparation of N-(Cyclohex-1-enyl) Pyridinium Salts **(4.39)**.

The appropriate 1-(2-Bromocyclohexyl)pyridinium salt **(4.38)** (7 mmole) and pyridine (3 ml) in nitromethane (25 ml) were heated under reflux for 32 hrs. After removing all the volatile matter under reduced pressure, the residue was dissolved in CH_2Cl_2 (25 ml) and treated with NH_3 gas for 5 min. The precipitate formed was centrifuged and ethyl acetate (100 ml) added to the CH_2Cl_2 layer forming a precipitate. The supernatent liquid was carefully decanted and the residual solid extracted with boiling acetone (30 ml). Addition of ether (100 ml) to the acetone extract reprecipitated the desired products which were filtered, washed thoroughly with ether and dried (60°C at 15 mm of Hg). The following pyridinium salts were made by this procedure:

1-(Cyclohexen-1-yl)-4-methylpyridinium bromide **(4.39a)**.

From 1-(2-Bromocyclohexyl)-4-methylpyridinium bromide **(4.38a)**. Yield : 1.25 g (70%); δ_H (D_2O, DSS as internal standard) 9.1 (2H, d, J 7 Hz), 8.3 (2H, d, J 7 Hz), 6.6 (1H, m), 2.8 (3H, s) and 2.7-1.6 (8H, m).

1-(Cyclohexen-1-yl)-3,5-dimethylpyridinium bromide (4.39b).

From 1-(2-Bromocyclohexyl)-3,5-dimethylpyridinium bromide (4.38b). Yield : 1.3 g (70%); δ_H (D_2O, DSS as internal standard) 8.9 (2H, s), 8.6 (1H, s), 6.5 (1H, m) and 2.8-1.6 (14H, m).

1-(Cyclohexen-1-yl)-4-phenylpyridinium bromide (4.39c).

From 1-(2-Bromocyclohexyl)-4-phenylpyridinium bromide (4.38c). Yield : 2.2 g (90%); δ_H (DMSO-d_6) 9.5 (2H, d, J 8 Hz), 8.8 (2H, d, J 8 Hz), 8.7-8.3 (2H, m), 8.1-7.8 (3H, m), 6.7 (1H, m) and 2.9-1.6 (8H, m).

Sodium Borohydride Reduction of N-(Cyclohehexen-1-yl) pyridinium Salts (4.39).

A solution of $NaBH_4$ (0.02 g, 0.5 mmole) in water (5 ml) (adjusted to pH 10 with 10% aqueous NaOH) was added dropwise to a suspension of the appropriate N-cyclohexenylpyridinium bromide (4.39) (2 mmole) in ether (15 ml) at 0°C. After 3 hr at room temperature, water (10 ml) was added and the ether layer separated. The aqueous layer was extracted with ether (10 ml). The combined ether fractions was washed with brine (10 ml) and dried (Na_2SO_4). Removal of solvent under reduced pressure gave the crude N-cyclohexenyldihydropyridines which were characterized through their ^{1}H-NMR spectra. The following dihydropyridines were prepared according to this general procedure:

1-(Cyclohexen-1-yl)-4-methyl-1,2-dihydropyridine **(4.41)**.

Prepared from 1-(Cyclohex-1-yl)-4-methylpyridinium bromide **(4.39a)** as a yellow oil. Crude yield : 0.25 g (71%); δ_H ($CDCl_3$) 6.5 (1H, d, J 8 Hz), 5.1 (1H, m), 4.5-4.9 (2H, m), 4.2 (2H, d, J 3 Hz) and 2.5-1.4 (11H, m).

1-(Cyclohexen-1-yl)-3,5-dimethyl-1,2-dihydropyridine **(4.42)** and 1-(Cyclohexen-1-yl)-3,5-dimethyl-1,4-dihydropyridine **(4.43)**.

From 1-(Cyclohexen-1-yl)-3,5-dimethylpyridinium bromide **(4.39b)** as a yellow oil. Crude yield of the mixture : 0.28 g (70%); characteristic δ_H ($CDCl_3$) for (4.33) : 6.3 (1H, s), 5.7 (1H, m), 4.6 (1H, m) and 3.9 (2H, s); characteristic δ_H ($CDCl_3$) for (4.34) : 6.1 (1H, s), 5.1 (1H, m) and 2.7 (2H, s).

Preparation of 1-(Cyclohexen-1-yl)-4-phenyl-1,2-dihydropyridine **(4.44)**.

$NaBH_4$ (0.02 g, 0.5 mmole) in water (3 ml) (adjusted to pH 10 with 10% aqueous NaOH) was added dropwise at 0°C to a suspension of 1-(Cyclohexen-1-yl)-4-phenylpyridinium bromide **(4.39c)** (0.67 g, 2 mmole) in CH_3CN (5 ml). After 2 hrs at room temperature, water (15 ml) was added and the yellow precipitate was filtered, washed with water and crystallized from CH_3CN to give yellow needles (0.42 g, 85%), m.p. 138-140°C (decomp.) (Found: C, 86.12, H, 8.15, N, 5.83. $C_{17}H_{19}N$ requires C, 86.03, H, 8.07, N, 5.90%). δ_H (DMSO-d_6)

7.5-7.2 (5H, m), 6.5 (1H, d, J 8 Hz), 5.5 (1H, m), 5.1 (1H, dd, J 8 Hz, J 2 Hz), 4.6 (1H, m), 4.2 (2H, d, J 4 Hz) and 2.4-1.4 (8H, m). δ_C (DMSO-d_6) 138.9, 138.1, 134.2, 129.3, 127.7, 126.5, 124.7, 109.6 (C-3), 100.4 (C-5), 95.5 (C-2'), 46.8 (C-2), 25.6, 23.9, 22.5 and 21.8.

Pyrolysis of 1-(Cyclohexen-1-yl)-4-phenyl-1,2-dihydropyridine **(4.44)**.

The 1,2-dihydropyridine **(4.44)** (0.5 g, 2 mmole) was heated at 160°C in a Kughelrohr apparatus under 0.1 mm of Hg. After 4 hrs the white sublimate was collected which proved to be 4-phenylpyridine (0.06 g, 20%); m.p. 69-71°C (lit. m.p. 69-70°C); δ_H ($CDCl_3$) 8.7 (2H, d, J 8 Hz) and 7.8-7.4 (7H, m).

CHAPTER V

THERMAL BEHAVIOR OF 1,2-DIHYDROPYRIDINES WITH UNSATURATED 4-SUBSTITUENTS

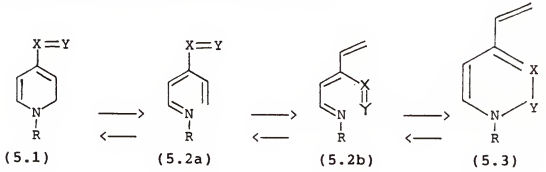
5.1. Introduction

The thermal behavior of 1,2-dihydropyridines was discussed in chapter IV. A striking feature was their electrocyclic ring opening to 1-azatrienes. We were interested in the potential utilization of these highly reactive 1-azatrienes in non-degenerate electrocyclic processes. It was envisaged that thermal electroreversion of a 4-vinyl-1,2-dihydropyridine would produce a cross-conjugated tetraene (Scheme 5.1). The latter showed promise of undergoing interesting electrocyclic processes.

Scheme 5.1

5.1.1. Aim of the work

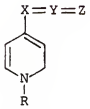
Thermal ring opening of a 4-vinyl-1,2-dihydropyridine (**5.1**) would lead to the cross-conjugated tetraene (**5.2a**). Electrocyclization of tetraene **5.2a** in its isomeric form **5.2b** would afford a new dihydropyridine (**5.3**) in which the elements X and Y of the original 4-vinyl substituent are now incorporated in the ring (Scheme 5.2). However (**5.3**) is itself a 4-vinyl-1,2-dihydropyridine derivative and its thermal behavior would be expected to be very similar to (**5.1**) and the sequence shown in Scheme 5.2 can therefore be considered as an equilibrium process.



Scheme 5.2

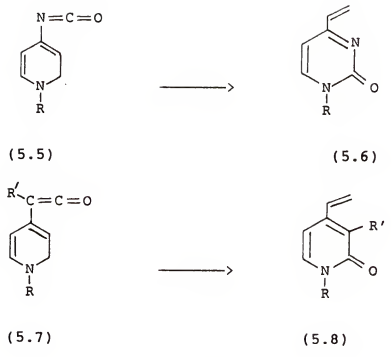
Such an equilibrium may be driven forward if sufficient stability be imparted to **5.3** so as to prevent its cycloreversion. The stability of **5.3** would be highly dependent on the 4-substituent in **5.1** since the elements of the latter become part of the ring-skeleton in **5.3**. Thus the

success of the proposed transformation rested on the proper choice of 4-substituents in 5.1. A cummulative double bond at the 4-position of 5.1 appeared ideally suited for this purpose. On this basis, a model dihydropyridine (5.4) can be drawn which shows the essential features required for our starting material.



(5.4)

The cummulated function could either be an isocyanate group (as in 5.5) or a ketene function (as in 5.7) which would eventually lead to the 2-pyrimidinone (5.6) and the 2-pyridone (5.8) derivatives, respectively (Scheme 5.3). Both 2-pyrimidinone and 2-pyridone posess certain degree of aromaticity and are more stable than 1,2-dihydropyridines. Thus the systems (5.5) and (5.7) were chosen to study the proposed set of thermal transformations.



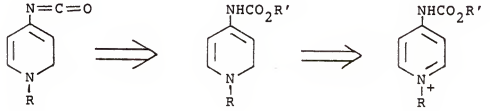
Scheme 5.3

5.2. Results and Discussion

5.2.1. Synthetic Strategy

As a possible route to the desired 1,2-dihydropyridines, $NaBH_4$ reduction of the corresponding pyridinium salts was considered. It was well anticipated that a selective reduction of the pyridinium ring in 4-isocyanatopyridinium salts would be far from simple. Therefore, a suitable isocyanate precursor was needed which would be inert to

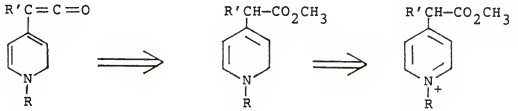
$NaBH_4$ reduction. A logical choice was the carbamate function which is one of the known precursors to isocyanates and is also inert to $NaBH_4$. This allowed for a convenient retrosynthesis of the 4-isocyanato-1,2-dihydropyridine (5.5) as shown in Scheme 5.4.



(5.5)

Scheme 5.4

Based on similar arguments, a methyl acetate group was chosen as a possible precursor to the ketene function for 4-keteno-1,2-dihydropyridine (5.7). A possible retrosynthetic route for the latter is shown in Scheme 5.5.

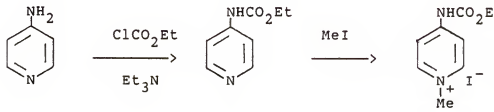


(5.7)

Scheme 5.5

5.2.2. Preparation of 4-Ethoxycarbonylaminopyridinium Salt

We first studied the synthetic route to the 4-isocyanatopyridinium salt. We started with ethyl 4-pyridylcarbamate **(5.9)** which was easily prepared from 4-aminopyridine according to literature procedure [58CA(52)18475g, 62JCS2379]. The corresponding methiodide **(5.10)** was prepared in 98% yield by treatment with excess MeI in refluxing ethanol (Scheme 5.6)



(5.9) **(5.10)**

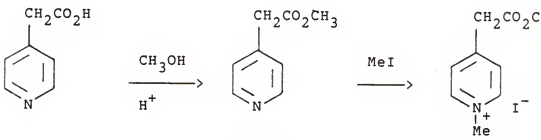
Scheme 5.6

5.2.3. Attempted Sodium Borohydride Reduction of 4-Ethoxycarbonylaminopyridinium Salt

Even under strenuous conditions (refluxing MeOH), $NaBH_4$ failed to reduce the pyridinium salt **(5.10)**. This may be attributed to the electron releasing effect of the amino function at the 4-position of the pyridinium ring. In order to diminish this effect, a second electron withdrawing group on the 4-amino function was considered. However the desired 4-(bis-ethoxycarbonyl)aminopyridine could not be prepared as the sodio-salt of **5.9** failed to react with diethyl carbonate or ethyl chloroformate.

5.2.4. Preparation of 4-Methoxycarbonylmethyl-1-methyl pyridinium Salt

Turning to the 4-keteno series, we started with methyl 4-pyridylacetate (5.11) [55JCS2586] which was prepared by the acid catalyzed esterification of the commercially available 4-pyridylacetic acid. Treatment with MeI in refluxing ethanol produced the corresponding methiodide (5.12) [64AJC455] in 70% yield (Scheme 5.7).



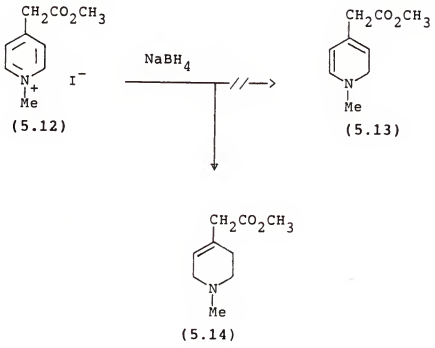
(5.11) (5.12)

Scheme 5.7

5.2.5. Sodium Borohydride Reduction of 4-Methoxycarbonylmethyl-1-methylpyridinium Salt

Sodium borohydride reduction of the pyridinium salt (5.12) was attempted in order to prepare the desired 1,2-dihydropyridine (5.13). Reduction in methanol, at -78°C, afforded an oil whose ^{1}H-NMR spectrum gave no indication for the presence of a 1,2-dihydropyridine moeity. Reduction under biphasic conditions (CH_2Cl_2-H_2O) [77H593] also gave

the same result. Based on its ^{1}H-NMR data, a tetrahydropyridine structure **(5.14)** was assigned to this product (Scheme 5.8).

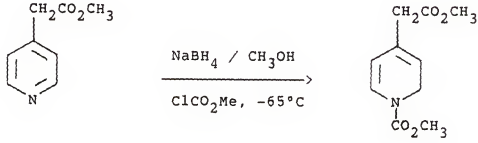


Scheme 5.8

The ^{1}H-NMR of **(5.14)** showed a one proton multiplet at δ 6.1 assigned to the vinylic hydrogen while a complex multiplet (4H) at 2.8 - 3.1 ppm was assigned to the C-5 methylene and the exocyclic methylene protons. The methyl ester produced a singlet at 3.6 ppm (3H); an unresolved multiplet at δ 2.1 - 2.7 accounted for the remaining aliphatic hydrogens and the N-CH_3.

5.2.6. Preparation of 1-Methoxycarbonyl-4-methoxycarbonylmethyl-1,2-dihydropyridine

Sodium borohydride reduction of N-alkylpyridinium salts, most often, are accompanied by over-reduction to the tetrahydropyridines [86AHC(39)1]. Since no easy solution exists, we turned our attention to Fowler's method [72JOC1321] of preparing 1,2-dihydropyridines directly from the corresponding pyridines. Thus the previously described 4-methoxycarbonylmethylpyridine (5.11) was treated with $NaBH_4$ (-65°C, MeOH) in presence of methyl chloroformate which produced the novel 1,2-dihydropyridine (5.15) in 87% yield (Scheme 5.9).



(5.11) (5.15)

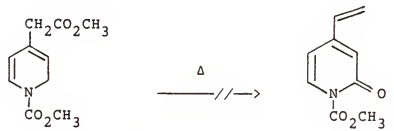
Scheme 5.9

The ^{1}H-NMR spectrum of (5.15) showed two doublets, one for the H-2 protons at δ 4.4 (2H, J = 4 Hz) and the other for the H-6 proton at δ 6.8 (J = 8 Hz). The H-3 and H-5

protons formed a multiplet around δ 5.1-5.5. The methyl ester and the methyl carbamate produced a pair of singlets at δ 3.7 and 3.8 whereas a broad singlet at δ 3.0 (2H) was assigned to the exocyclic methylene protons. This novel 1,2-dihydropyridine **(5.15)** may be purified by flash chromatography (neutral alumina, $CHCl_3$ eluent) and is stable upto 24 hrs at 0°C under nitrogen.

5.2.7. Thermolysis of 1-Methoxycarbonyl-4-methoxycarbonylmethyl-1,2-dihydropyridine

Thermolysis of the 1,2-dihydropyridine **(5.15)** was performed in chlorobenzene. After heating at 160°C in a sealed tube for 12 hrs, the ^{1}H-NMR spectrum still showed the presence of unreacted dihydropyridine; the desired 2-pyridone derivative **(5.16)** could not be observed even after prolonged heating (24 hrs) at that temperature (Scheme 5.10). When the thermolysis was carried out at a higher temperature (200°C for 12 hrs), it only led to extensive decomposition.



(5.15) **(5.16)**

Scheme 5.10

5.3. Conclusions

The dihydropyridine 5.15 failed to undergo the proposed rearrangement. This was attributed to its inability to undergo ring-opening to the cross-conjugated aza-tetraene. No further variations were attempted.

5.4. Experimental

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM 360L instrument. Chemical shifts are reported in δ (ppm) values downfield from Me_4Si. Elemental analyses (C, H, N, F) were carried out by Dr. R. W. King of this department. Removal of solvent under reduced pressure refers to solvent evaporation on a rotary evaporater connected to an water aspirator.

The following compounds were prepared according to known literature procedures:

4-Ethoxycarbonylaminopyridine (5.9), m.p. 127-129°C (lit. [58CA(52)18475g, 62JCS2379] m.p. 129°C);

4-Methoxycarbonylmethylpyridine (5.11), b.p. 72-73°C/0.5 mm (lit. [55JCS2586] b.p. 85-87°C/1.5 mm);

4-Methoxycarbonylmethyl-1-methylpyridinium iodide (5.12), m.p. 136-137°C (lit. [64AJC455] m.p. 141-142°C);

4-Ethoxycarbonylamino-1-methylpyridinium iodide (5.10).

4-Ethoxycarbonylaminopyridine (5.9) (5.0 g, 30 mmole) and methyl iodide (12.7 g, 90 mmole) in ethanol (15 ml) was heated under reflux for 12 hrs. On cooling to room temperature the methiodide (5.10) crystallized out which was filtered and washed with cold ethanol. Recrystallization from ethanol gave white plates (9.1 g, 98%); m.p. 189-190°C (Found: C, 34.83, H, 4.18, N, 8.81. $C_9H_{13}IN_2O_2$ requires C, 35.08, H, 4.25, N, 9.09%); δ_H (DMSO-d_6) 11.6 (1H, broad), 8.9 (2H, d, J 7 Hz), 8.0 (2H, d, J 7 Hz), 4.5-4.1 (5H, m) and 1.3 (3H, t, J 9 Hz).

Sodium Borohydride Reduction of 4-Methoxycarbonylmethyl-1-methylpyridinium iodide (5.12).

At 0°C, a solution of $NaBH_4$ (0.06 g, 2.5 mmole) in methanol (2 ml) was added to a solution of the methiodide (5.12) (2.93 g, 10 mmole) in methanol (10 ml). After 1.5 hrs at 0°C, water (20 ml) was added and the reaction extracted with ether (3 X 15 ml). The combined organic layer was dried (Na_2SO_4) and removal of solvent under reduced pressure gave an oil (1.3 g, 80%); δ_H ($CDCl_3$) 5.7 (1H, m), 3.7 (3H, s), 3.1-2.8 (4H, m) and 2.6-2.0 (7H, m).

Methyl (1-methoxycarbonyl-1,2-dihydropyridin-4-yl)acetate **(5.15)**.

To a mixture of $NaBH_4$ (0.38 g, 10 mmole) and methyl 4-pyridylacetate **(5.11)** (1.51 g, 10 mmole) in dry methanol was added slowly a solution of methyl chloroformate (0.94 g, 10 mmole) in dry ether (10 ml) at -78°C. After 3 hrs at -65°C it was added to crushed ice and extracted with CH_2Cl_2 (3 X 15 ml). The combined organic layer was washed with saturated NH_4Cl solution (10 ml) followed by brine (10 ml) and dried (Na_2SO_4). Removal of solvent under reduced pressure gave an oil. This was purified by flash chromatography over a short column of neutral alumina ($CHCl_3$ as eluent). The yellow oil thus obtained (1.83 g, 87%) was stored under nitrogen at 0°C ; δ_H ($CDCl_3$) 6.8 (1H, d, J 8 Hz), 5.5-5.1 (2H, m), 4.4 (2H, d, J 4 Hz), 3.8 (3H, s), 3.7 (3H, s) and 3.0 (2H, s).

CHAPTER VI

SUMMARY

The effect of heteroatoms on an all-carbon skeleton was outlined in chapter I. The reactivity patterns of the α-carbons in amines and alcohols was discussed, with particular reference to the generation of carbanions at those centers. In addition, thermal electrocyclic ring-opening of 1,3-cyclohexadiene and its heteroatom modified derivative, 1,2-dihydropyridine was compared. A preview of the present investigation was also provided.

In chapter II, the concept of transient activation of an α-sp^3 center toward proton loss in secondary amines was discussed. In a novel approach, carbon dioxide was utilized as a protecting group for the α-metallation of indoline and tetrahydroquinoline. The lithium carbamates derived from these two amines, however, did not offer much α-activation; nevertheless, α-metallation was achieved with a combination of potassium t-butoxide and t-butyllithium. The α-metallo species were trapped with aldehydes and ketones (other electrophiles gave poor results) and afforded the

α-substituted amines directly after acidic work-up. The advantages of this procedure over the existing three step sequence are that the protecting group was easily introduced and deprotection occurred under very mild conditions (during acidic work-up); also, the whole set of operations was conveniently carried out in the same reaction vessel without the need to isolate any intermediates.

Carbon dioxide was next applied as a hydroxyl protecting group for the generation of α-oxycarbanions which was described in chapter III. Although its protecting ability was successfully demonstrated, the α-activating power of the derived lithium carbonates was extremely small, if any. This called for the utilization of an easily removable α-activating auxilliary, a role which was aptly fulfilled by the trimethylsilyl group. Thus it was shown that the commercially available 1-trimethylsilylmethanol *via* its lithium carbonate can be successfully α-lithiated with *s*-butyllithium. The resulting α-lithio species reacted with esters (including α,β-unsaturated derivatives), amides, acid chlorides to give the corresponding α-hydroxy ketones after acidic work-up. Thus the combination of carbon dioxide protecting group and the trimethylsilyl auxilliary led to the development of a methanol dianion synthon, a species difficult to generate.

In chapters IV and V, the thermal electrocyclic ring-opening of 1,2-dihydropyridines was investigated. It was envisaged that the derived 1-azatrienes from N-vinyl- or 4-vinyl-1,2-dihydropyridines would participate in further electrocyclic processes to give interesting products. In order to study this, two novel N-cyclohexenenyl-1,2-dihydropyridines were synthesized via the borohydride reduction of the corresponding pyridinium salts as was described in chapter IV. However the pyrolysis of these dihydropyridines did not afford any products resulting from their ring-opened form and instead, oxidation to the pyridine bases took place. For the 4-vinyl-series, the thermal behavior of the 4-methoxycarbonylmethyl-1,2-dihydropyridine was studied which was discussed in chapter V. In this case also, the dihydropyridine was found to be highly resistant toward its thermal ring-opening and under drastic conditions, extensive decomposition occurred.

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Letter Codes for Journal Titles

Code	Journal Abbreviation
ACR	Acc. Chem. Res.
ACS(B)	Acta Chim. Scand., Ser. B.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.

AJC	Austr. J. Chem.
BSF	Bull. Soc. Chim. France.
CA	Chem. Abstr.
CB	Chem. Ber.
CC	J. Chem. Soc., Chem. Commun.
CI(L)	Chem. Ind. (Lond.)
CJC	Can. J. Chem.
CL	Chem. Lett.
CRV	Chem. Rev.
CZ	Chem. -Ztg.
H	Heterocycles
HCA	Helv. Chim. Acta.
JA	J. Am. Chem. Soc.
JCS	J. Chem. Soc.
JCS(PI)	J. Chem. Soc., Perkin Trans. 1.
JHC	J. Heterocycl. chem.
JMR	J. Mag. Reson.
JOC	J. Org. Chem.
JPS	J. Polym. Sci.
LA	Liebigs Ann.
MI	Miscellaneous
OM	Organometallics
PAC	Pure Appl. Chem.
S	Synthesis
T	Tetrahedron
TL	Tetrahedron Lett.

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BIOGRAPHICAL SKETCH

Saumitra Sengupta was born on the Christmas Eve of 1957 in Calcutta, India. After receiving his primary education in three different cities while travelling with his family, he graduated with B.Sc. (Hons.) and M.Sc. (specialization in organic chemistry) degrees in chemistry from Jadavpur University at Calcutta. After a brief period of research at Jadavpur, he joined the University of Florida as a graduate student in the Fall of 1982. He is a recipient of the National Merit Scholarship from the Government of India and is a member of the American Chemical Society, Indian Chemical Society and the Indian Association for the Cultivation of Science.

I certify that I have read this study and that in my opinion it confirms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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